STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

Submitted in partial fulfillment of the requirements
for the award of the degree

M.D. GENERAL MEDICINE

BRANCH -1

to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

APRIL 2015

CERTIFICATE BY THE GUIDE

This is to certify that this dissertation in **" STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE "**is a bonafide research work done by **Dr. REETA JAMES**, under my guidance towards partial fulfilment of regulations of The Tamilnadu Dr.M.G.R. Medical University, Chennai.

Professor & Head of the Dept.
Dr. N. KUMAR NATARAJAN MD
Department of General Medicine
Coimbatore Medical College

Professor & Guide :
Dr. S. CHANDRASEKHARAN MD
Department of General Medicine
Coimbatore Medical College

Date :

THE DEAN
Coimbatore Medical College

Coimbatore Medical College

COIMBATORE, TAMILNADU, INDIA - 641 014

(Affiliated to The Tamilnadu Dr. MGR Medical University, Chennai)

ETHICS COMMITTEE

CERTIFICATE

Name of the Candidate : REETA JAMES

Course : M.D GENERAL MEDICINE

Period of Study : 2012 - 2015

College : COIMBATORE MEDICAL COLLEGE.

Dissertation Topic : STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

The Ethics Committee, Coimbatore Medical College has decided to inform that your Dissertation Proposal is accepted / ~~Not accepted~~ and you are permitted / ~~Not permitted~~ to proceed with the above Study.

DEAN
Coimbatore Medical College & Hospital,
Coimbatore.

DECLARATION

I solemnly declare that this dissertation entitled **" STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE "** is a bonafide and genuine research work carried out by me at Coimbatore Medical College and Hospital during the academic year 2012-2015 under the guidance and supervision of **Dr. S. CHANDRASEKHARAN MD,** Professor, Department of Medicine, Coimbatore Medical College Hospital, Coimbatore.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University, towards the partial fulfilment of requirement for the award of M.D.Degree in General Medicine (Branch-I).

Place:

Date: **Dr. REETA JAMES**

ACKNOWLEDGEMENT

First of all, I thank the Almighty for his many blessings and for the silver linings around every cloud I saw.

With utmost respect, I express my deepest gratitude to my guide and my Chief, **Prof. Dr. S. Chandrasekharan MD**. He has been a great teacher and a constant source of inspiration throughout the course. I thank him for his valuable guidance and suggestions in the making of this dissertation.

I would like to extend my respect and gratitude to the Head of the Department of Medicine, **Prof. Dr. N. Kumar Natarajan MD**, for his support and inspiration during the course as well as in the dissertation work. I also thank **Prof. Dr. N. Sundar MD**, for his help in choosing the topic of study and motivation for proceeding with the study as well as updating ourselves with the latest in the field of medicine.

I also express my heartfelt thanks to my Assistant Professors, **Dr. S. Avudaiappan MD**, **Dr. K. Sivakumar MD**, **Dr. A. Nilavan MD** and **Dr. B. Vetriveeran MD** for their support and guidance and for the wonderful teachers they have been.

I am extremely grateful to The Dean, Coimbatore medical college, **Dr. S. Revwathy MD DNB OG**, for her support and for permitting to utilize the resources of this hospital for my thesis work. I am also thankful to the administration and allied departments for their help and cooperation in carrying out my study.

From the depth of my heart, I express my sincere thanks to my fellow postgraduates and roommates for their help and companionship during the course. I fall short of words to thank my parents for their unconditional support and sacrifices through all these years, without which, my postgraduation would not have been the same.

Last, but definitely not the least, I express my heartfelt gratitude to my patients. Without their cooperation, my course would not have been fruitful and this study, impossible.

Dr. REETA JAMES

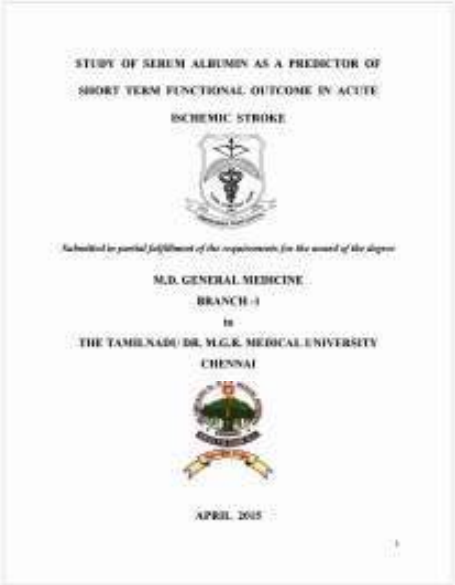
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	201211316.md General Medicine RE...
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	STUDY OF SERUM ALBUMIN AS A...
File name:	INTRODUCTION.docx
File size:	919.39K
Page count:	103
Word count:	11,169
Character count:	65,906
Submission date:	22-Sep-2014 10:51PM
Submission ID:	452898467



STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

Submitted in partial fulfillment of the requirements for the award of the degree

M.D. GENERAL MEDICINE
BRANCH -I
to
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI

APRIL 2015


https://turnitin.com/dv?s=1&o=452898467&u=1030975808&student_user=1&lang=en_us&
The Tamil Nadu Dr M.G.R Medical...
TNMGRMU EXAMINATIONS - DUE 15-A...
Originality
GradeMark
PeerMark
STUDY OF SERUM ALBUMIN AS A
turnitin
17%
SIMILAR
--
OUT OF 0
STUDY OF SERUM ALBUMIN AS A PREDICTOR OF
SHORT TERM FUNCTIONAL OUTCOME IN ACUTE
ISCHEMIC STROKE
Submitted in partial fulfillment of the requirements for the award of the degree
M.D. GENERAL MEDICINE
BRANCH - I
to
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI
Match Overview
1 bja.oxfordjournals.org Internet source 5%
2 www.uic.edu Internet source 2%
3 J. P. Nicholson. "The r... Publication 2%
4 www.med.yale.edu Internet source 1%
5 Submitted to University... Student paper 1%
6 14.139.159.4:8080 Internet source 1%
7 Gerald B. Appel. "The ... Publication <1%
8 Submitted to University... Student paper <1%
PAGE: 1 OF 103
Text-Only Report
start
8:19 PM

ABBREVIATIONS

ACA	:	Anterior Cerebral Artery
CAD	:	Coronary Artery Disease
CNS	:	Central Nervous System
CT	:	Computerised Tomography
DM	:	Diabetes mellitus
ECG	:	Electrocardiogram
GCS	:	Glasgow Coma Scale
IL	:	Interleukin
MCA	:	Middle Cerebral Artery
MRI	:	Magnetic Resonance Imaging
MRS	:	Modified Rankin Scale
PET	:	Positron Emission Tomography
SHT	:	Systemic Hypertension
SSS	:	Scandinavian Stroke Scale
TIA	:	Transient Ischemic Attack
TNF α	:	Tumour Necrosis Factor alpha
TOAST	:	Trial Of Org in Acute Stroke Treatment

TABLE OF CONTENTS

LIST OF TABLES

LIST OF CHARTS

LIST OF FIGURES

ABSTRACT

Background & Objectives :

Stroke is a life threatening neurological disorder. Identification of predictors of mortality is vital so that prompt therapeutic measures can be instituted to improve outcome. Animal studies have shown neuroprotective effect of albumin in ischemic stroke. But this has not been studied well enough in humans to recommend supplementation of albumin as a therapeutic measure in stroke. The objective of this study is to determine the association between the serum albumin at admission and the stroke severity as well as functional outcome at 7days.

Methods :

The study was done over a period of 6 months and included 100 subjects with first ever stroke which was proved to be ischemic by CT Brain. After a detailed history and clinical examination, lab investigations including serum albumin were sent. Patients with history of previous stroke and those with conditions predisposing to hypoalbuminemia were excluded from the study. The severity of stroke was measured using Scandinavian Stroke Scale and the functional status at 7days was assessed using modified Rankin scale. Statistical analysis was done to determine

the association between serum albumin and stroke severity as well as functional outcome and to find out the correlation between these.

Results :

There was no significant variation in serum albumin with age and sex. There was definite association between serum albumin at admission and the severity of stroke. There was negative correlation between serum albumin value and the MRS score thereby indicating better outcome with higher albumin level. So the study concludes that higher the serum albumin, lesser the stroke severity and better the prognosis.

Key words:

Serum albumin, Ischemic stroke, outcome, nutrition

INTRODUCTION

Stroke or cerebrovascular accident is a life threatening neurological disorder. It constitutes more than 50% of admissions in a hospital. It has been estimated that by the year 2020, stroke will emerge as the second leading cause of morbidity and mortality in developed countries. Westernization of lifestyle and the resulting demographic transition might increase the burden of stroke in developing countries as well.

Early mortality from stroke is mostly directly related to stroke. Complications affect mortality only later in the course. Previous studies have thrown light on the various risk factors of stroke as well as the factors which influence mortality, some of which may serve as predictors of mortality. Stroke severity, type of stroke, increased age, level of consciousness etc. are few of them. But most of these are non-modifiable and hence of limited value in clinical practice. Identification of predictors of mortality, especially, modifiable ones, is vital so that prompt therapeutic measures can be instituted to improve outcome.

Albumin is a multifunctional protein which has been proven to have neuroprotective effects in animal studies. Albumin is also an indicator of the nutritional status. This fact holds importance, as, out of

15 million stroke events occurring annually all over the world, two third occurs in low income and middle income developing countries, where malnutrition is rampant.

There have been several studies in the western world including interventional studies trying to explore the scope of albumin as a neuroprotective agent. Some of these have shown that albumin therapy is capable of minimizing infarction volume and cerebral oedema. Albumin reduces hematocrit as well as erythrocyte sedimentation rate by its affects on erythrocyte aggregation. Effect of albumin is mainly in the early reperfusion phase of acute ischemic stroke where it exerts an inhibitory effect on stagnation, thrombosis and leucocyte adhesion in microcirculation.

There is very little data from our part of the world regarding the role of albumin in ischemic stroke. Through my study, I intend to determine the association, if any, between serum albumin and the severity as well as the short term outcome of acute ischemic stroke. The study has been undertaken with the foresight that if the association can be proven beyond doubt, it may be possible to institute corrective measures in order to improve the prognosis of the disease.

AIMS & OBJECTIVES

1. To measure the stroke severity at admission using Scandinavian Stroke Scale.

2. To assess the functional outcome of ischemic stroke on day 7 using Modified Rankin Scale.

3. To find out the association between serum albumin at admission and the functional outcome of ischemic stroke.

4. To find out the correlation between serum albumin level and severity of ischemic stroke.

REVIEW OF LITERATURE

Stroke is one disease that has revolutionised the field of neuromedicine. No other disease has contributed to our present understanding of brain like stroke. Human brain is the most complex structure known, composed of 100 billion neurons forming trillions of connections with other brain cells[1]. The integrity of these connections is inevitable for the integrative power of the brain. There are a thousand different symptoms that can occur following a stroke depending on the part of the brain and the blood vessel involved[2]. The devastating disability that results is mainly due to the inherent inability of the brain cells to regenerate. The patterns of neurological deficits that manifest when a particular area of the brain is affected was noted by physicians centuries ago. But it took years of clinical observation supported by advances in neurophysiology and imaging to reach the present stage. So literally, generations of neurologists have learnt the brain, stroke by stroke[3].

A GLIMPSE OF HISTORY

Hippocrates, the Father of Medicine, first identified stroke over 2400 years ago. Term 'Apoplexia' was used by Greeks to denote a disease where the patient falls to the ground without sense or voluntary

motion. Victims were referred to as 'Attoniti' (Latin, meaning thunderstruck)[4] or 'Syderati' (meaning planet struck)[5]. Doctors then had little knowledge of the anatomy and function of brain, the cause of this phenomenon or how to treat it.

Supernatural Theory

- Apoplexy was thought to be supernatural. Affected persons were thought to be struck with an invisible power and was referred to as 'dreadful visitation'.[6]

Humoral Theory

- Of the four humours, Hippocrates considered blood as the one that contained spirit/ vitality . Apoplexy was thought to be due to stagnation/ station of blood[7].

- Galen also accepted the theory of Hippocrates. According to him, apoplexy was caused by interference to flow of the 'vital spirit' to the brain[8].

- Bloodletting was practiced as a treatment of apoplexy.

- Robinson suggested that bleeding was useful to decrease the Plethora and relieve the pressure on animal organs. But in case of

'Phlegmatick Apoplexy' in which there are features of blood impoverishment, bleeding could kill than save[9].

- By nineteenth century, when the concept of blood pressure was accepted, measures to decrease arterial blood pressure as a treatment of apoplexy were discussed and venesection was thought to rapidly and effectively achieve this. This practice was discontinued only after it was published in 'Osler's Principles and Practice Of Medicine' that venesection was not beneficial in practice and may even be deleterious[10].

- The concept of Apoplectic habitus is comparable to the modern concept of obese habitus in individuals susceptible to cardiovascular disease[11].

In mid 1600's, Jacob Webfer found that patients who died of apoplexy had either bled in the brain or had occlusion of one of the cerebral blood vessels[12].

In 1928, apoplexy was classified based on the nature of blood vessel affection and the new terminology- 'stroke' / 'cerebrovascular accident' came into use.

Stroke is now often referred to as Brain Attack due to the resemblance in basic pathology to heart attack. The purpose of the new term is to alert the layman regarding the need for urgent attention.

RELEVANT ANATOMY

All the arteries supplying the brain are branches of the brachiocephalic arteries arising from the aorta. The common carotid arteries of both sides ascend the anterior neck and bifurcate at the level of the angle of mandible forming internal and external carotid arteries. The Internal Carotid Artery with its tributaries, the Middle cerebral Artery(MCA) and the Anterior Cerebral Artery (ACA) forms the anterior circulation which perfuses the entire frontal and parietal lobes and most part of temporal lobes[13].

Posterior circulation (Vertebrobasilar system) is formed from the right and left vertebral arteries which are branches of the subclavian artery arising from the aorta. They ascend within the vertebral foramen and loop over the transverse process of C1 vertebra and enter the skull via foramen magnum. They join to form basilar artery at the level of pons. Basilar artery bifurcates at the level of midbrain forming the right and left posterior cerebral arteries. The Vertebrobasilar system with its

perforating branches perfuses the brainstem, cerebellum, thalamus, occipital lobe and part of temporal lobe[13].

At the base of brain, the major arteries meet to form the Circle Of Willis where the Anterior Cerebral Artery and the Middle Cerebral Artery are linked to the Posterior Cerebral Artery by Anterior and Posterior Communicating arteries. This anastomosis forms the communication between the anterior and posterior circulations and between the right and left sides of the brain[14].

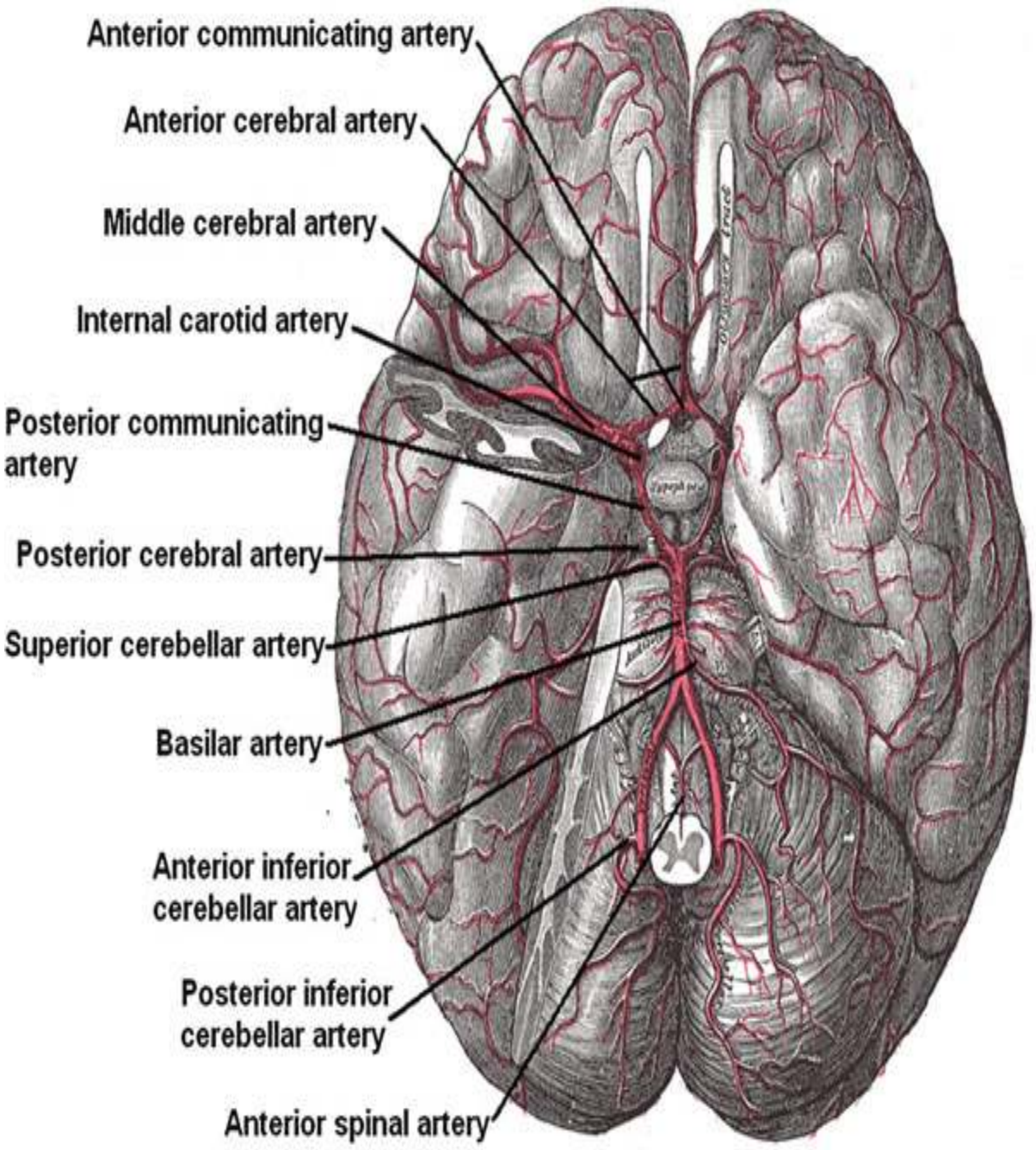


Figure 1: Cerebral Circulation

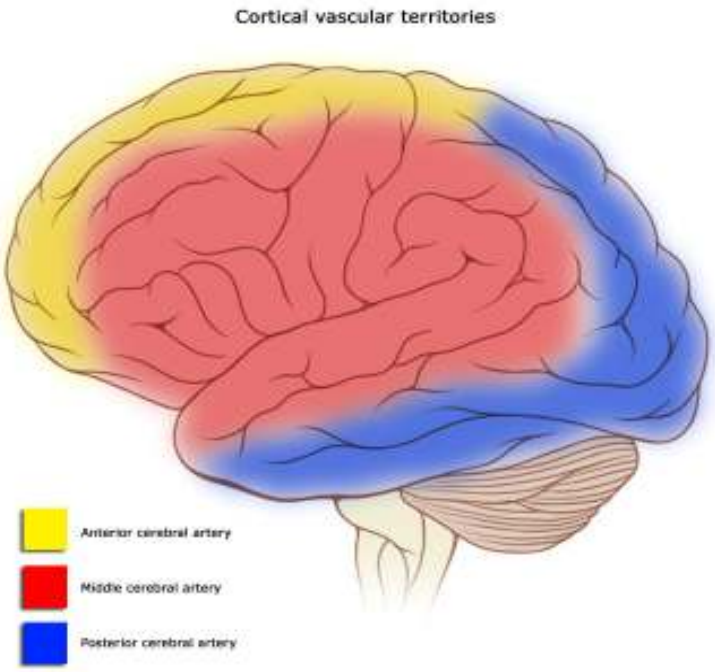


Fig 2 : Cortical vascular territories- lateral aspect

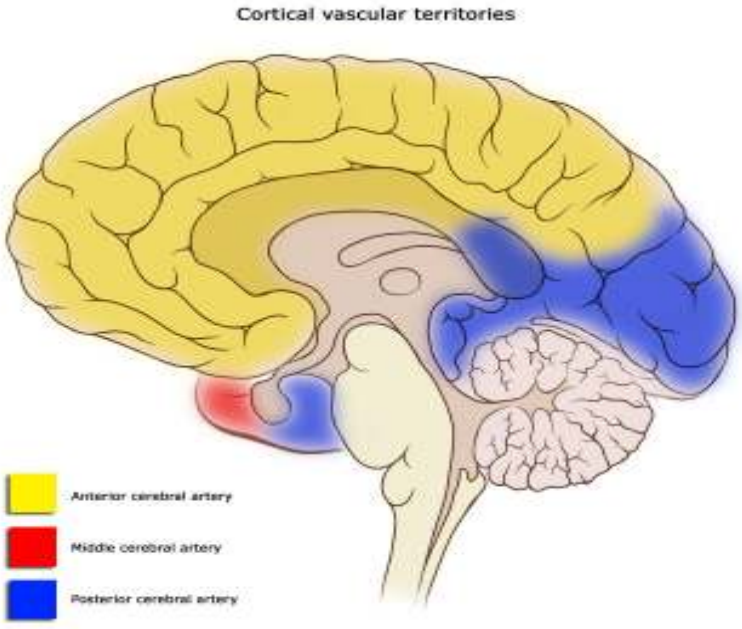


Fig 3: Cortical Vascular Territories- medial aspect

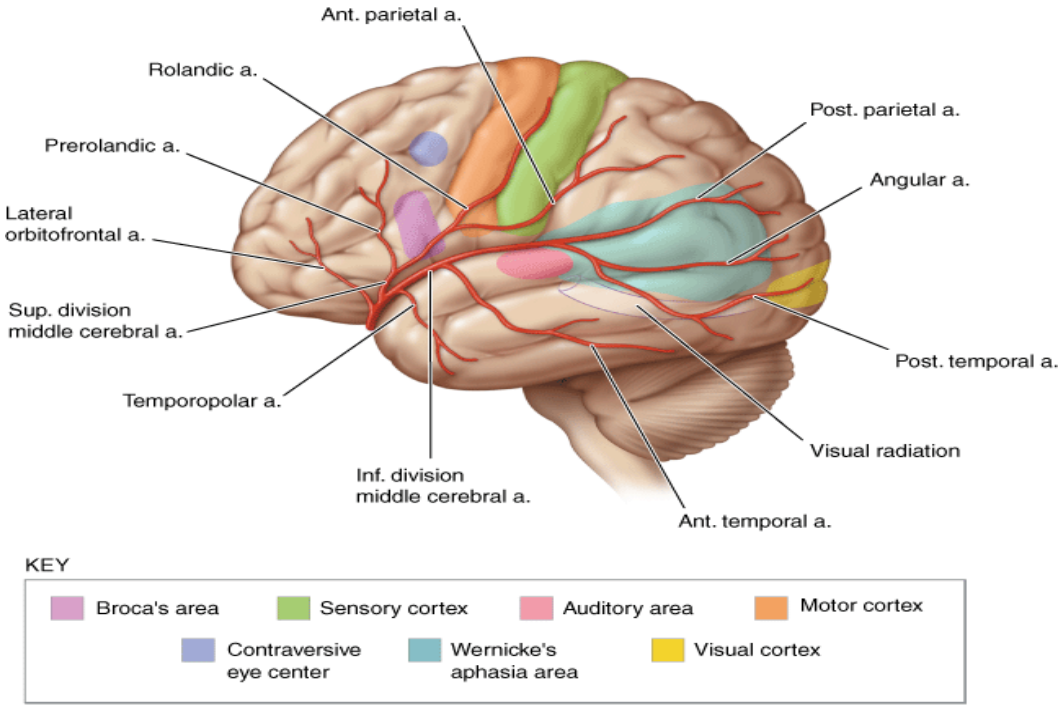


Figure 4: Areas of brain- lateral aspect

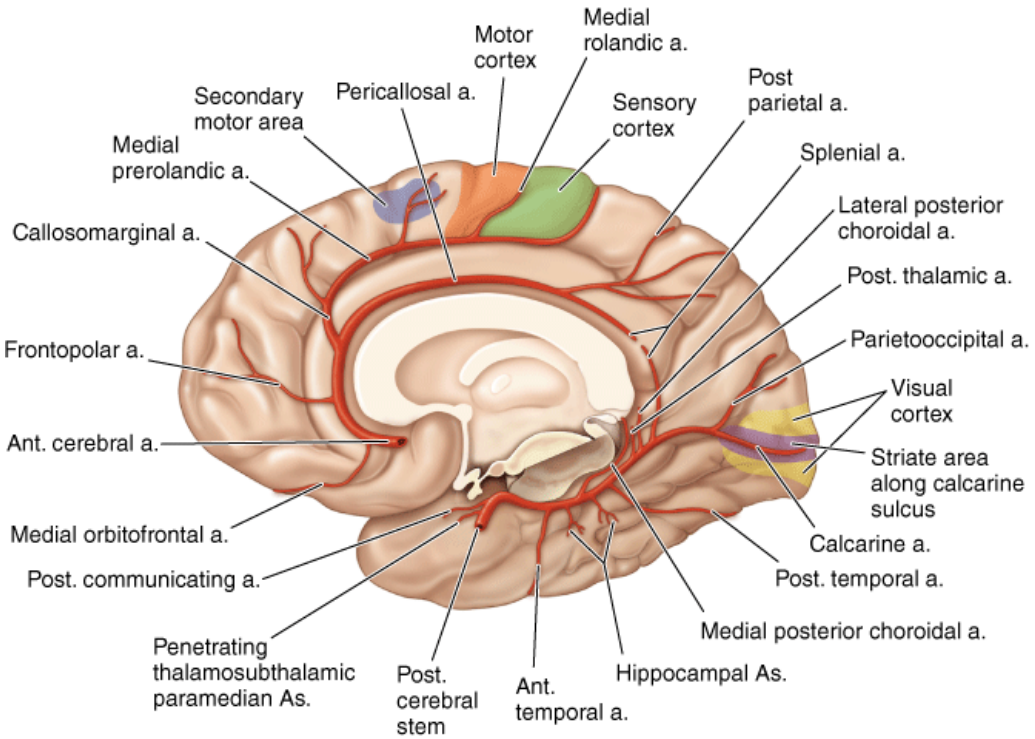


Figure 5: Areas of brain- medial aspect

WHO DEFINITION OF STROKE

Rapidly developing clinical symptoms or signs of focal or global loss of cerebral function with symptoms lasting for more than 24hrs or leading to death with no apparent cause other than that of vascular origin.

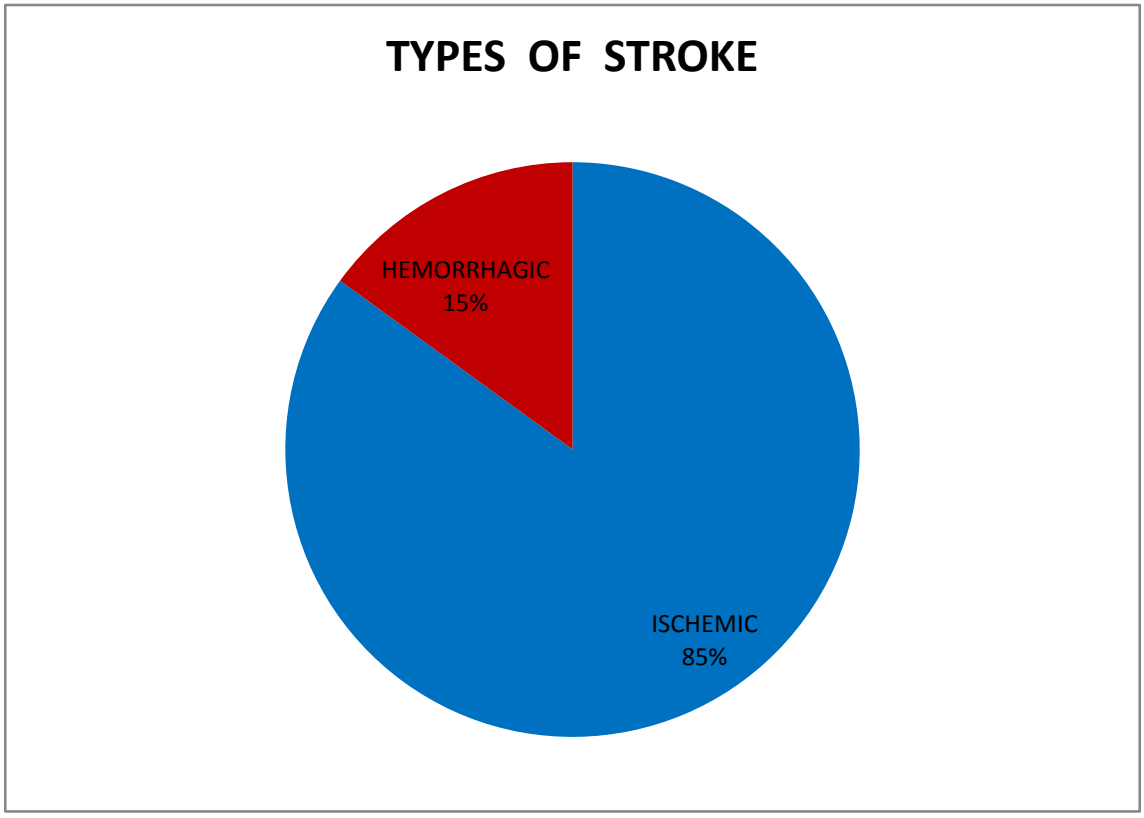


Chart 1: Types of stroke

HEMORRHAGIC STROKE

Types

- Subdural /epidural hemorrhage : Produced by trauma
- Subarachnoid hemorrhage : Due to trauma or rupture of intracranial aneurysm
- Intraparenchymal hemorrhage

INTRAPARENCHYMAL HEMORRHAGE

- Most common type : Intracerebral hemorrhage[15]
- Causes
    - Hypertension
    - Trauma
    - Cerebral amyloid angiopathy
    - Cocaine and amphetamine use (in young)
    - Coagulopathy
    - AV malformation
    - Metastatic brain tumour

ISCHEMIC STROKE

ETIOLOGY

- Thrombosis
    - Large vessel thrombosis
    - Lacunar stroke (small vessel)
    - Dehydration
- Embolic occlusion
    - ✓ Artery to artery
        - Carotid bifurcation
        - Aortic arch
        - Arterial dissection
    - ✓ Cardioembolic
        - Atrial fibrillation
        - Mural thrombus
        - Myocardial infarction
        - Dilated cardiomyopathy
        - Valvular lesions : Mitral stenosis

          Mechanical valve

Infective endocarditis

- ✓ Paradoxical embolus : Atrial septal defect

  Patent foramen ovale

- ✓ Atrial septal aneurysm

- ✓ Spontaneous echo contrast

UNCOMMON CAUSES	
❖ Hypercoagulable disorders Protein C deficiency Protein S deficiency Antithrombin III deficiency Antiphospholipid syndrome Factor V Leiden mutation Prothrombin G20210 mutation Systemic malignancy Sickle cell anemia Thalassemia Polycythemia vera Systemic lupus erythematosus Homocysteinemia Thrombotic thrombocytopenic purpura Disseminated intravascular coagulation Dysproteinemias	❖ Vasculitis Systemic vasculitis [PAN, granulomatosis with polyangiitis (Wegener's), Takayasu's, giant cell arteritis] Primary CNS vasculitis Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster) ❖ Cardiogenic Mitral valve calcification Atrial myxoma Intracardiac tumor Marantic endocarditis Libman-Sacks endocarditis ❖ Subarachnoid hemorrhage vasospasm

Nephrotic syndrome Inflammatory bowel disease Oral contraceptives ❖ Venous sinus thrombosis ❖ Fibromuscular dysplasia	❖ Drugs: cocaine, amphetamine ❖ Moyamoya disease ❖ Eclampsia

Table 1: Uncommon causes of ischemic stroke

PATHOPHYSIOLOGY OF ISCHEMIC STROKE

CEREBRAL BLOOD FLOW

- Normal cerebral perfusion is about 50-60ml/100g/min[15]

The effects of brain ischemia are rapid as there is no stored glucose and neurons are incapable of anaerobic metabolism. In response to ischemia, cerebral autoregulatory mechanisms come into play by local vasodilatation, opening of collaterals and increased utilisation of oxygen and glucose from blood.

- A decrease in cerebral perfusion to zero leads to death of brain tissue within 4-10minutes.
- A decrease to less than 10ml/100g/min culminates in irreversible neuronal injury

- A decrease to less than 16-18ml/100g/min results in infarction within an hour

- When cerebral blood flow decreases to less than 20ml/100g/min, an electrical silence ensues with a decrease in synaptic activity in an attempt to preserve energy stores. This results in ischemia without infarction unless this situation is extended for several hours or days[16].

If reperfusion occurs prior to significant amount of cell death, there may be only transient symptoms and this is referred to as Transient Ischemic Attack (TIA). The standard definition of TIA requires all the neurological signs and symptoms to resolve within 24hours regardless of whether there is imaging evidence of new permanent brain injury[15].

A generalized reduction in cerebral blood flow due to systemic hypotension usually causes syncope. If the low blood flow persists longer, infarction develops in the borderzone of major artery territories. Severe global hypoxia ischemia causes extensive brain injury referred to as Hypoxic Ischemic Encephalopathy[15].

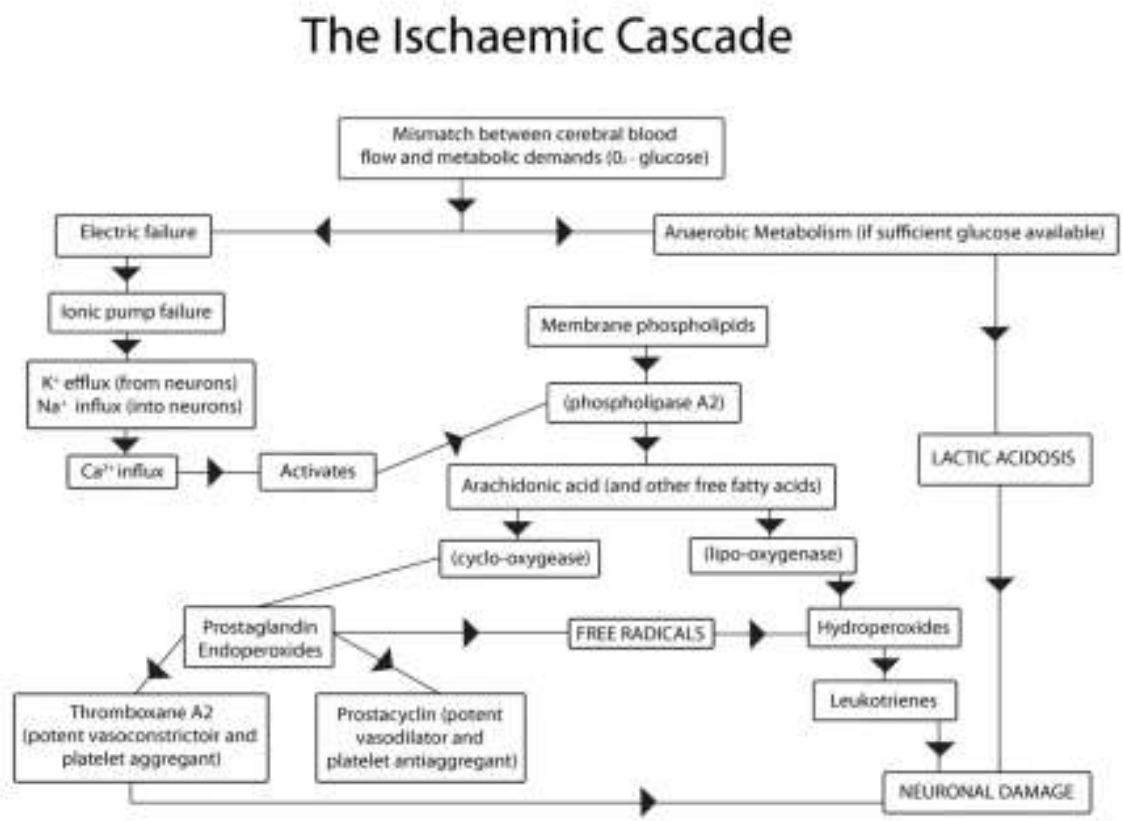


Figure 6 : Mechanism of ischemic injury

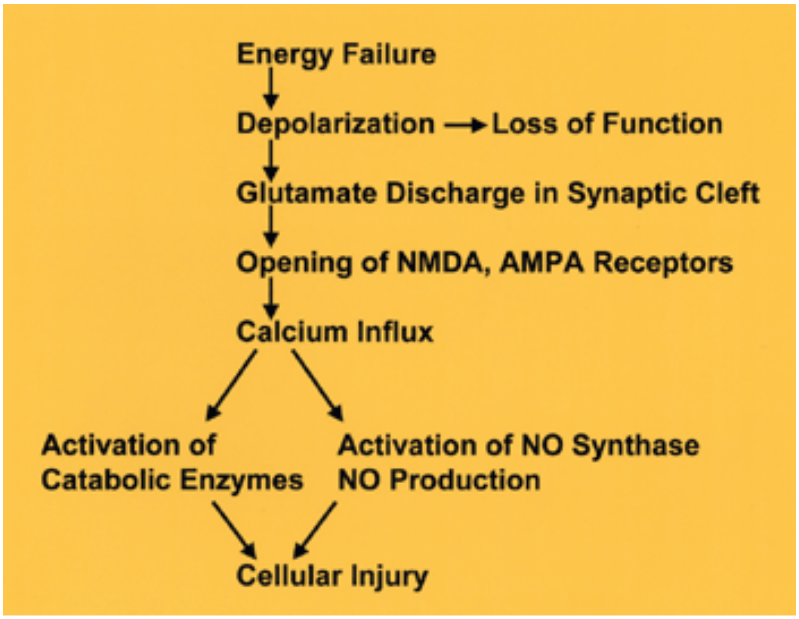


Figure 7: Mechanism of ischemic cellular injury

FOCAL ISCHEMIC INJURY

Vascular occlusion by thrombus or embolus can cause ischemia of the affected vascular territory. At gross tissue level, vascular compromise causes acute ischemia or infarction which is a dynamic process evolving over time. At cellular level, hypoxia causes neuronal injury.

NEURONAL INJURY

Ischemia triggered activation of destructive vasoactive enzymes released by endothelium, leucocytes, platelets and other neuronal cells promote the formation of microthrombus which occludes the cerebral microcirculation[17].

At molecular level, occurrence of hypoxic ischemic neuronal injury is mainly influenced by the overaction of neurotransmitters – glutamate and aspartate. This process is called excitotoxicity[18]. It is triggered by depletion of cellular energy stores. Glutamate is normally stored in synaptic terminals. It is cleared from the extracellular space by an energy dependent process. Hence in an energy depleted state, there is an higher concentration of glutamate and aspartate in the extracellular space. This causes the opening of calcium channels associated with N-Methyl-D-Aspartate (NMDA) and Alpha- Amino-3-Hydroxy-5-Methyl-4-Isoxanole propionate (AMPA) receptors. Persistent membrane depolarization

results in influx of calcium, sodium and chloride ions and efflux of potassium ions[19]. Increased intracellular calcium induces activation of several destructive enzymes like proteases, lipases and endonucleases. These permit the release of cytokines and other mediators which end up destroying the cellular integrity[20].

Inflammatory response to tissue injury is mediated by various inflammatory mediators among which Tumour Necrosis Factor is the key agent. Leucocyte recruitement to ischemic areas occurs within 30 minutes of ischemia and reperfusion. Leucocytes activate vasoactive substances like oxygen free radicals, arachidonic acid metabolites (cytokines) and nitric acid. These cause vasodilatation, vasoconstriction, more permeability, enhanced platelet aggregation, increased leucocyte adhesion to the endothelial wall and immunoregulation.

First to respond to hypoxia are endothelial cells. The response is morphological, biochemical and immunological causing a variety of physiological and pharmacological effects. Endothelial cells swell and form microvilli on the luminal surface. This causes a narrowing of luminal patency of capillary vessels. As a result, mechanical plugging by erythrocytes, leucocytes and platelets ensues[21].

Endothelial cells mediate the effects of vasoactive agents like endothelin peptides, eicosanoids and smooth muscle relaxants such as nitric acid. These agents alter vascular tone of the microcirculation. The key process in the initiation of the inflammatory process, namely leucocyte adherence to the endothelial wall, is brought about by activation of endothelial adhesion molecules.

ISCHEMIC PENUMBRA

Within an hour of hypoxic ischemic insult, an oligemic zone called ischemic penumbra develops around a core of infarction, where the autoregulation is ineffective. In this area, cellular integrity and some amount of energy metabolism is preserved. Neurological deficits due to ischemia in this region can be partially or fully reversed by reperfusing within a critical time period (2-4hrs) called the Window Of Opportunity[22].

Pathophysiology of ischemic penumbra is closely related to generation of Spontaneous Waves of Depolarisation (SWD). These are multifocal in origin, some arising from the core of infarction, some from the penumbra. They are associated with sustained increase in synaptic glutamate and extracellular potassium[23]. Hypoxic/ rapid depolarizations supervene just before irreversible neuronal death.

NEURONAL DEATH

Occurs by 2 processes- Coagulation necrosis and Apoptosis

Apoptotic mechanisms start within an hour of ischemic injury whereas necrosis sets in about 6hours after arterial occlusion.

Coagulation Necrosis

Rapid breakdown of cellular cytoskeleton principally due to energy failure. Attributed to effects of physical, chemical and osmotic damage to plasma membrane. Cell initially swells, then shrinks and undergoes pyknosis over 6-12hrs. By 24hours, extensive chromolysis occurs resulting in pannecrosis. Astrocytes swell and fragment, myelin sheath degenerates[16].

Apoptosis

In this, cells are programmed to die. Nuclear damage is the first to occur. Integrity of plasma membrane and mitochondrial membrane are preserved till the last. Ischemia causes activation of latent suicide proteins in the nucleus which triggers the autolytic processes culminating in cell death. This autolytic process is involves DNA cleavage[24].

Ischemia starves the neuron of glucose and oxygen leading to failure of mitochondria to produce ATP. In the absence of ATP, membrane ion pumps stop functioning leading to depolarization of neurons and increase in intracellular calcium. Cellular depolarization causes increased glutamate release from the synaptic terminals. Excess glutamate activates postsynaptic glutamate receptors which enhance neuronal calcium influx resulting in neurotoxicity. Free radicals formed by membrane lipid degradation and mitochondrial dysfunction result in catalytic destruction of the membrane and damage other vital functions of the cell.

Progression and extent of ischemic injury depends on[25]

(i) Rate of progression and onset : Short duration and slow onset strokes are better tolerated.

(ii) Collateral circulation : Good collateral circulation correlates with better outcome

(iii) Health of systemic circulation : Constant cerebral perfusion pressure depends on adequate systemic blood pressure

(iv) Hematological factors : Hypercoagulable state causes exacerbation of vascular occlusion by increasing progression and extent of thrombus

(v) Temperature : Increased temperature causes greater ischemic injury

(vi) Glucose metabolism : Hyperglycemia adversely affects size of infarct

SUBCLASSIFICATION OF ISCHEMIC STROKE

TOAST CLASSIFICATION

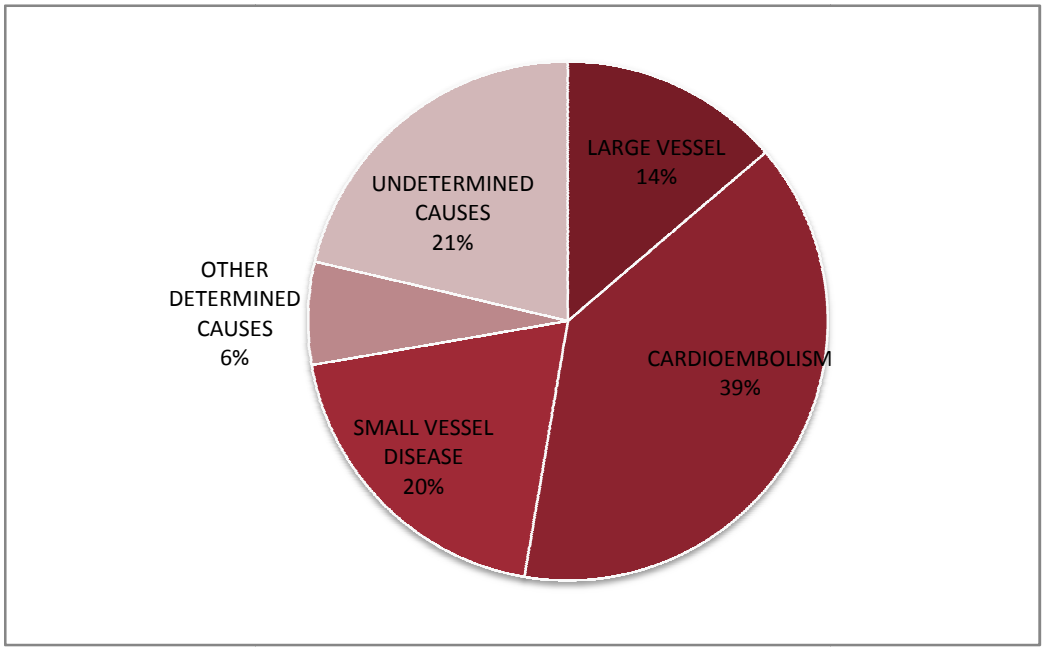


Chart 2: TOAST classification of ischemic stroke

LARGE VESSEL ATHEROTHROMBOSIS

Involves both intracranial and extracranial arteries.

Atherosclerosis is the most common pathology underlying vascular occlusion causing thrombotic stroke[26]. There is formation of lipid laden atherosclerotic plaques on the inner wall of a large vessel. They form over a prolonged time course with the effect that the brain is able to adjust to the gradual reduction in cerebral blood flow[27]. Infarcts occur only when a critical level of stenosis is reached. These atherosclerotic plaques are susceptible to ulceration, thrombosis, calcification and intraplaque hemorrhage and the susceptibility depends on its structure, composition and consistency[28]. Depending on the vessels involved, location of the lesion within the affected vessel, rapidity of development and the presence or absence of anastomoses, it typically results in a single large territorial stroke.

Most common sites : Bifurcation of Common Carotid Artery[29]

Origin of Vertebral artery

Course of middle cerebral artery prior to bifurcation

Risk factors : Hypertension

Diabetes mellitus

Dyslipidemia

EMBOLIC STROKE

- Tend to be sudden in onset with maximum neurological deficit at onset
- Non rheumatic atrial fibrillation is the most common cause of cerebral embolism overall, the risk of which is calculated using CHADS2 score.

CARDIOEMBOLIC STROKE

- ✓ Occur due to embolism of thrombotic material on the atrial, ventricular or left heart valves.
- ✓ They usually occur in more than one arterial distribution, mostly anterior circulation[30].
- ✓ Acute strokes involving the right and left anterior circulation are considered embolic unless proven otherwise[31].

- ✓ The location and extent of the infarct depend on the extent of collateral circulation.

- ✓ The most common causes of cardioembolic stroke are Nonrheumatic/nonvalvular atrial fibrillation, myocardial infarction, prosthetic valves, rheumatic heart disease and ischemic cardiomyopathy

- ✓ In Paradoxical embolisation, a venous thrombus migrates into arterial circulation through an atrial septal defect or patent foramen ovale.

- ✓ Other than venous clot, fat emboli, tumour emboli, bacterial endocarditis, intravenous air and amniotic fluid emboli can also cause paradoxical embolisation.

ARTERY TO ARTERY EMBOLIC STROKE

- ✓ Thrombus formed on the wall of a particular vessel fragments and sheds pieces of clots. These are swept downstream and may lodge in smaller branches of the large arteries causing multiple smaller strokes within the territory of the parent vessel[32].

- ✓ Most common source of embolus : Carotid bifurcation atherosclerosis

- Carotid Atherosclerosis
  - Most common sites : Common Carotid bifurcation

    Proximal internal carotid artery
  - Risk factors : Male gender

    Old age

    Smoking

    Hypertension

    Diabetes

    Hypercholesterolemia
  - Classified based on degree of stenosis and whether stenosis is symptomatic or not.
- Intracranial atherosclerosis : Produces stroke either by insitu thrombosis or embolism
- Dissection of internal carotid or vertebral arteries
  - Trauma
  - Spinal manipulative surgeries

- Ehlers- Danlos type 4
- Marfan's disease
- Cystic medial necrosis
- Fibromuscular dysplasia

Neurological outcome of an embolic stroke depends on the affected vascular territory and the tendency of the embolus to cause vasospasm by acting as a vascular irritant. Vasospasm tends to occur in young patients since the vessels are more pliable and less atherosclerotic[33].

Many embolic strokes become hemorrhagic resulting in HEMORRHAGIC INFARCT (RED INFARCT)[34] where bleed occurs into the necrotizing cerebral tissue. Pathogenesis of hemorrhagic infarct is explained by 2 mechanisms[35]-

(i) Reperfusion of the ischemic tissue following spontaneous lysis of the embolus

(ii) In persistent occlusion of the vessel proximally, due to reperfusion from leptomeningeal vessels that form the collateral circulation.

Probability of hemorrhagic infarction depends on the size of the infarct, extent of collateral circulation and the use of anticoagulant and thrombolytic agent.

SMALL VESSEL STROKE

- ✓ LACUNAR INFARCTION
- ✓ Caused by occlusion of small penetrating arteries
- ✓ Involves the 30-300μm branches of the major cerebral arteries that penetrate the deep gray and white matter of the cerebrum or brainstem.
- ✓ Occlusion by atherothrombotic disease or lipohyalinotic thickening
- ✓ Small infarcts 3mm to 2cm diameter called lacunes
- ✓ Risk factors : Hypertension, age
- ✓ Pure motor stroke : 33-50% of all small vessel strokes
- ✓ A large vessel stroke may initially manifest as a lacunar syndrome

❖ Lacunar syndromes referable to posterior circulation[31]

- o Hemiballism
- o Hemichorea
- o Isolated dysarthria

LACUNAR SYNDROME	SITE OF INFARCT
PURE MOTOR HEMIPARESIS	POSTERIOR LIMB OF INTERNAL CAPSULE / BASIS PONTIS
PURE SENSORY STROKE	VENTRAL THALAMUS
ATAXIC HEMIPARESIS	VENTRAL PONS / INTERNAL CAPSULE
DYSARTHRIA AND CLUMSY HAND SYNDROME	VENTRAL PONS / GENU OF INTERNAL CAPSULE

Table 2: Lacunar syndromes

GLOBAL ISCHEMIA/ HYPOTENSIVE STROKE

- ✓ Occurs following drastic reduction in systolic BP due to any cause.
- ✓ Cerebral gray matter is particularly vulnerable
- ✓ The more susceptible neurons are the Purkinje cell layer of Hippocampus and Purkinje cell layer of the cerebellar cortex.
- ✓ Abundance of glutamate makes them more susceptible to global ischemia
- ✓ Global ischemia causes maximum damage to areas between the terrirories of the major cerebral and cerebellar arteries called the 'Boundary Zone' or 'Watershed Area'.

Watershed Infarct

- Develops in the region between the adjacent arterial territories which share a collateral circulation
- Parietotemporooccipital triangle at the junction of anterior, middle and posterior cerebral arteries is most commonly affected[36].
- Results in paralysis and sensory loss of the arm sparing the face and speech
- Comprises 10% of ischemic strokes
- 40% occur in carotid stenosis/occlusion

Borderzone/ Terminoterminal Infarcts[37]

Occurs between two arterial territories whose parent vessels do not share a collateral flow

STROKE DUE TO UNDETERMINED CAUSE

❖ Includes cases where complete workup and screening for cardiac conduction/ structural abnormalities, intracranial/ extracranial large artery occlusions, coagulopathies and other underlying conditions has been nonconclusive.

- ❖ Clinical situation where complete workup cannot be done is also included in this.

- ❖ Since they form a large share of strokes, newer subclassifications like ASCO and computer-aided SSS-TOAST have been proposed to study their outcomes and riskfactors[38].

CONDITIONS THAT MIMIC TIA / STROKE

- o Migraine
- o Seizure
- o Hypoglycemia
- o Brain tumor
- o Arteriovenous malformation
- o Multiple sclerosis
- o Incipient syncope
- o Orthostatic hypotension
- o Cardiac arrhythmia
- o Amnesia
- o Narcolepsy/cataplexy
- o Intracranial inflammation(Meningitis/ Encephalitis)

- Periodic paralysis
- Compressive neuropathy
- Dizziness of uncertain cause
- Anxiety
- Hyperventilation
- Labyrinthine disease

RISK FACTORS FOR STROKE

- **Definite**
  - Modifiable : Cigarette smoking
    Excessive alcohol consumption
    Drug use (cocaine, amphetamines)
  - Non modifiable : Age
    Sex
    Race
    Familial and genetic factors

- **Possible**
  - Oral contraceptive use
  - Diet
  - Personality type
  - Geographic location
  - Season
  - Climate
  - Socioeconomic factors
  - Physical inactivity
  - Obesity
  - Abnormal blood lipids
- **Disease or disease markers**
  - Hypertension
  - Cardiac disease
  - TIA
  - Elevated hematocrit
  - Diabetes mellitus
  - Sickle cell disease

- Elevated fibrinogen concentration
- Migraine headaches and migraine equivalents
- Carotid bruit

RISK FACTOR	RELATIVE RISK
HYPERTENSION	2-5
ATRIAL FIBRILLATION	1.8-2.9
DIABETES	1.8-6
SMOKING	1.8
HYPERLIPIDEMIA	1.8- 2.6
ASYMPTOMATIC CAROTID STENOSIS	2.0

Table 3 : Risk factors of ischemic stroke

HYPERTENSION

- Major risk factor for ischemic stroke
- Present in 50-70% of cases
- There is association between blood pressure and risk of stroke even at a systolic BP of 115mmHg

DIABETES

- Clear risk factor for 1st stroke
- Independent risk factor for recurrent stroke
- Predictor of multiple lacunar infarcts

DYSLIPIDEMIA

- Increased levels of total cholesterol and LDL-C are associated with higher risk of ischemic stroke[39]
- High serum triglyceride is independently associated with ischemic stroke especially large artery atherosclerotic strokes[40]
- Reduced HDL-C is also associated with greater risk of ischemic stroke

SMOKING

- Major independent risk factor for ischemic stroke
- Risk of stroke is also increased in exposure to passive smoking and tobacco smoke in the environment[41].
- Smoking facilitates atherosclerosis

- 5years after smoking cessation, stroke risk of ex-smoker is equal to that of nonsmoker

ALCOHOL

- Chronic alcoholism and heavy drinking bear a high risk for all stroke subtypes
- Studies have shown that there is a J shaped association between alcohol and ischemic stroke with the effect that there is protective effect in light or moderate consumption to increased risk in heavy consumption.
- The protective effect is due to raised HDL, decreased platelet aggregation and reduced concentration of plasma fibrinogen
- Increased risk is attributed to alcohol induced hypertension , hypercoagulable state, reduced cerebral blood flow and atrial fibrillation or cardioembolism due to cardiomyopathy
- Also plays a role in insulin resistance and metabolic syndrome.

OBESITY

- Body Mass Index > 30kg/m^2 is by itself a risk factor for cardiovascular disease
- Major role in primary prevention
- There are no studies to support that weight reduction may reduce the risk of recurrent stroke.

PHYSICAL ACTIVITY

- Exerts beneficial effect on various risk factors for stroke
- Physical activity reduces blood pressure and weight, enhances vasodilatation, improves glucose tolerance and promotes cardiovascular health.

METABOLIC SYNDROME

- Combination of several physiological abnormalities that increase risk of stroke.
- According to American Heart Association criteria, metabolic syndrome is recognized when 3 out of 5 features are present

(i) Increased waist circumference (>102cm in men and >88cm in women)

(ii) Increased triglycerides (>150mg/dl)

(iii) Decreased HDL-C (<40mg/dl in women and <50mg/dl in men)

(iv) Increased blood pressure (systolic >130mmHg or diastolic >85mmHg)

(v) Increased fasting blood glucose (>100mg/dl)

- Research has redefined the syndrome so as to include subclinical inflammation and disorders of thrombosis, fibrinolysis and endothelial function and theories suggest that it may be transmitted genetically[42].

HEART DISEASE

- The basic pathology being the same, if the coronaries are diseased, arteries to the brain are also likely to be affected

- Coronary artery disease, congestive heart failure, left ventricular hypertrophy, valvular heart disease and arrhythmias are all associated with graeter risk of stroke.

AGE

- Risk of stroke significantly increases with age
- The risk of stroke with advancing age cannot be changed, it has a prime role in assessing stroke risk and planning preventive therapies.

ORAL CONTRACEPTIVE PILLS

- Oestrogen promotes blood clotting
- Low dose oestrogen minimizes this risk

CAROTID BRUIT

- Noise due to turbulent flow in a blood vessel (artery) as a consequence of narrowing due to atherosclerosis
- Associated with high risk of ischemic stroke

INVESTIGATIONS

- Basic Investigations : Complete blood count

  Erythrocyte sedimentation rate

  Serum electrolytes

  Blood urea nitrogen

  Serum creatinine

  Blood sugar

  Urine analysis

  Serum lipid profile

- Electrocardiogram
- Chest Xray
- Coagulation profile : Prothrombin time

  Activated partial thromboplastin time

- Echocardiogram

- **IMAGING STUDIES**

  - ❖ CT SCAN

    - ✓ Imaging modality of choice in acute stroke
    - ✓ Early identification or exclusion of hemorrhage
    - ✓ Identification of extraparenchymal hemorrhages, neoplasms, abcesses and other conditions mimicking stroke
    - ✓ Infarct may not be seen reliably for 24 to 48 hours
    - ✓ Small ischemic strokes in the posterior fossa are not seen.
    - ✓ Small infarcts on the cortical surface are missed.

  - ❖ CONTRAST ENHANCED CT SCAN

    - ✓ Picks up subacute infarcts
    - ✓ Allows visualization of venous structures
    - ✓ Highlights the deficits in brain perfusion and shows regions of infracted brain as well as ischemic penumbra
    - ✓ Carotid disease and intracranial vascular occlusions are picked up with CT angiography

❖ MRI SCAN

- ✓ Reliably detects the extent and location of infarct in all areas of brain including posterior fossa and cortical surface
- ✓ Less sensitive to detect acute bleed
- ✓ Diffusion weighted imaging more sensitive for early brain infarction
- ✓ MR perfusion studies using Gadolinium contrast pick up ischemic penumbra
- ✓ MR angiography detects stenosis of extracranial internal carotid arteries and large intracranial arteries with high sensitivity.
- ✓ MRI with fat saturation visualizes extra or intracranial arterial dissection
- ✓ After the acute period, MRI clearly defines the extent of tissue injury and demarcates areas of old infarction from new.
- ✓ Highly sensitive to identify areas of new infarction in transient ischemic attacks

❖ CONVENTIONAL XRAY CEREBRAL ANGIOGRAPHY

- ✓ Considered gold standard in identifying and quantifying stenosis of cerebral arteries due to atherosclerosis
- ✓ CT angiography of entire head and neck may be used in the initial evaluation of stroke.
- ✓ Also identifies aneurysms, vasospasm, intraluminal thrombi, arteriovenous fistula, vasculitis, fibromuscular dysplasia and collaterals
- ✓ Drawbacks :
  - Arterial damage
  - Groin hemorrhage
  - Embolic stroke
  - Contrast nephropathy
- ✓ Conventional angiography coupled with endovascular techniques is employed in cerebral revascularization

❖ ULTRASOUND TECHNIQUES

- ✓ B mode ultrasound imaging is coupled with Doppler ultrasound for flow assessment (Duplex ultrasound)
  - Identifies and quantifies stenosis at origin of internal carotid artery
- ✓ Transcranial Doppler
  - Assesses flow in middle cerebral artery, anterior cerebral artery, posterior cerebral artery and vertebrobasilar system.
- ✓ Combination of MR angiography with these ultrasound studies used in evaluating vascular stenosis

❖ PERFUSION TECHNIQUES

- ✓ Xenon CT and PET
  - Assess and quantify cerebral blood flow
  - Help in the planning of revascularization surgeries
- ✓ Single photon emission computed tomography (SPECT)
  - Measures relative cerebral blood flow

- ✓ CT perfusion imaging
    - When combined with non contrast CT scan, detects ischemia and ischemic penumbra with increased sensitivity
- ✓ MR perfusion imaging
    - Demarcates the ischemic penumbra when combined with MR diffusion imaging

TREATMENT

Immediate Goal : Ensuring perfusion to the ischemic penumbra

Later Goals : Minimising disability

Preventing complications

Preventing recurrence

A. MEDICAL SUPPORT

- ❖ Blood pressure
    - ✓ Acute blood pressure lowering controversial as collateral blood flow is blood pressure dependent
    - ✓ Indications for blood pressure lowering

- Malignant Hypertension
- Concomitant myocardial ischemia
- BP > 185/110mmHg
- Planning for thrombolytic therapy

❖ Fever

✓ Detrimental

✓ Treated with antipyretics and surface cooling

❖ Serum Glucose

✓ Maintained at <110mg/dl

✓ Insulin infusion used if necessary

❖ Cerebral Oedema

✓ Peaks on 2^{nd} or 3^{rd} day

✓ Causes mass effect for near 10 days

✓ More likely with larger infarcts

✓ Treated with fluid restriction and IV mannitol which raise serum osmolarity

- ✓ Hypovolemia to be avoided as the resulting hypotension may worsen the infarction
- ✓ Trials have shown that hemicraniectomy markedly reduces mortality
- ✓ Cerebellar Infarction
    - Even small amounts of cerebellar oedema can severely raise the intracranial pressure
    - Cerebellar oedema may directly compress the brainstem causing coma and respiratory arrest
    - Emergency surgical decompression may be required
    - Prophylactic suboccipital decompression of large cerebellar infarcts is practiced in stroke centers

❖ Infections

- ✓ Pneumonia, urinary tract infections and bedsores are the common ones encountered
- ✓ Prevented by avoiding aspiration, physiotherapy and prophylactic antibiotics when required

- ✓ Use appropriate antibiotics when needed

❖ Deep Vein Thrombosis and Pulmonary Embolism

Prevented using :

- ✓ Pneumatic compression stockings
- ✓ Subcutaneous heparin

B. INTRAVENOUS THROMBOLYSIS

❖ INDICATIONS

- o Clinical diagnosis of ischemic stroke
- o Onset of symptoms to time of drug administration ≤3hours
- o CT scan showing no hemorrhage or oedema of > $1/3^{rd}$ of the MCA territory
- o Age ≥ 18years
- o Consent by the patient or surrogate

❖ Contraindications

- Sustained BP > 185/110mmHg despite treatment
- Platelet < 1,00,000
- Hematocrit < 25%
- Glucose <50 or >400mg/dl
- Use of heparin within 48hours and prolonged PTT or elevated INR
- Rapidly improving symptoms
- Prior stroke or head injury within 3months
- Prior intracranial hemorrhage
- Major surgery in preceeding 14days
- Minor stroke symptoms
- Gastrointestinal bleeding in preceeding 21days
- Recent myocardial infarction
- Coma or stupor

C. ENDOVASCULAR TECHNIQUES

- ✓ Intraarterial administration of thrombolytic agent
  - For large clots in the major vessels which fail to open with thrombolysis
  - Not yet approved by US FDA
- ✓ Endovascular Mechanical Thrombectomy

  Indications :
  - Ineligible or with contraindications to thrombolytics
  - Failed vascular recanalisation with IV thrombolytics

D. ANTITHROMBOTIC TREATMENT

- ❖ Platelet Inhibitors
  - Aspirin is the only antiplatelet drug proved to be effective in acute ischemic stroke
  - Use of aspirin within 48hours of stroke onset decreases risk of stroke recurrence and mortality

- Abciximab, a glycoprotein IIb/IIIa receptor inhibitor, should be avoided in acute stroke as it causes intracranial hemorrhage.

❖ Anticoagulation

- The routine use of heparin or other anticoagulants in atherothrombotic stroke is not supported by trials.

E. NEUROPROTECTION

✓ Measures that attempt to prolong the brain's tolerance to ischemia

- Hypothermia
- Drugs that block excitatory amino acid pathways

F. STROKE CENTERS

✓ A dedicated stroke team improves neurologic outcome and reduces mortality

✓ Emergency 24hour evaluation of patients with acute stroke and considering thrombolysis or endovascular treatments

G. REHABILITATION

- ✓ Includes early physical, occupational and speech therapy
- ✓ Involves educating the patient and family about patient's neurological deficit and on prevention of complications
- ✓ Aims to maximize recovery
- ✓ Restraint therapy : Immobilizing the affected side improves hemiparesis

This shows that physical therapy recruits unused neural pathways and the fact suggests that the human nervous system is more adaptable than originally thought.

ALBUMIN

Albumin Superfamily

- Serum Albumin
- Vitamin D binding protein
- Alpha Fetoprotein
- Alpha Albumin (Afamin)

- ✓ Most abundant plasma protein
- ✓ 55-60% of serum protein
- ✓ 585 aminoacids which form a single polypeptide chain, with a deficiency of tryptophan and methionine residues and an excess of charged residues
- ✓ Molecular weight : 66,500Da
- ✓ Xray crystallography reveals tertiary structure of human albumin crystal
- ✓ Heart shaped molecule $80 \times 30\ A^0$
- ✓ Highly flexible molecule which changes shape readily
- ✓ In solution, three domains are arranged in ellipsoid pattern forming low viscosity molecule
- ✓ Resilient structure which regains shape easily in physiological conditions due to the presence of disulphide bridges
- ✓ Denaturation occurs only in severe nonphysiological changes in temperature, pH and chemical environment

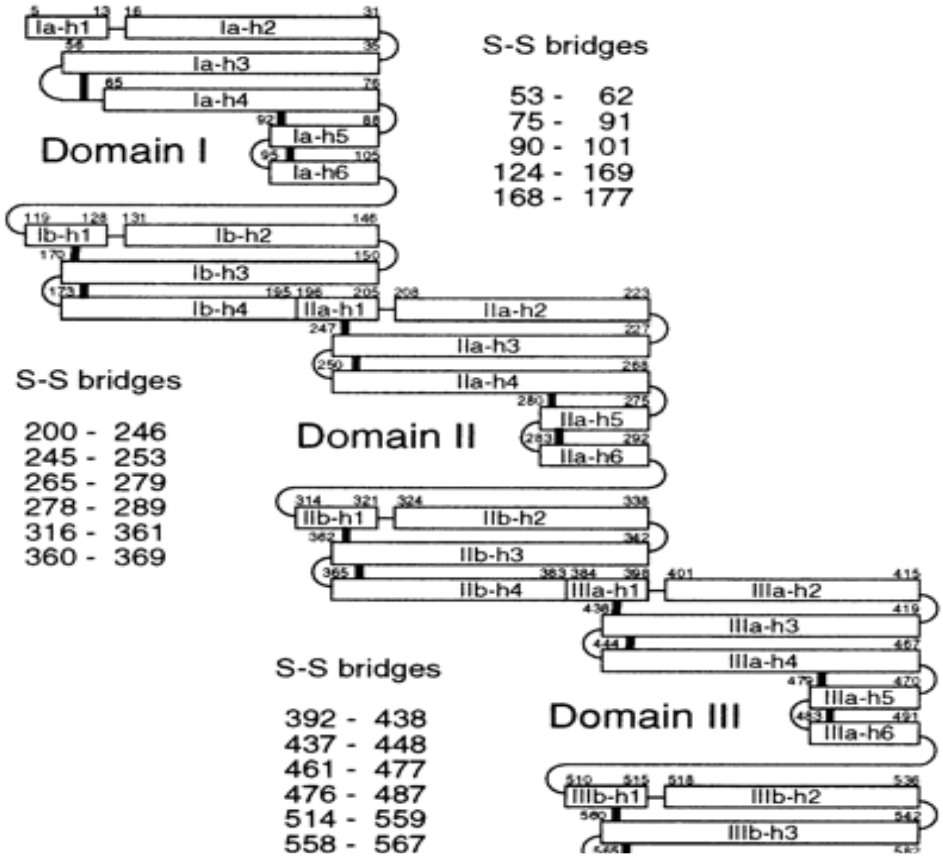


Figure 8: Tertiary structure of albumin

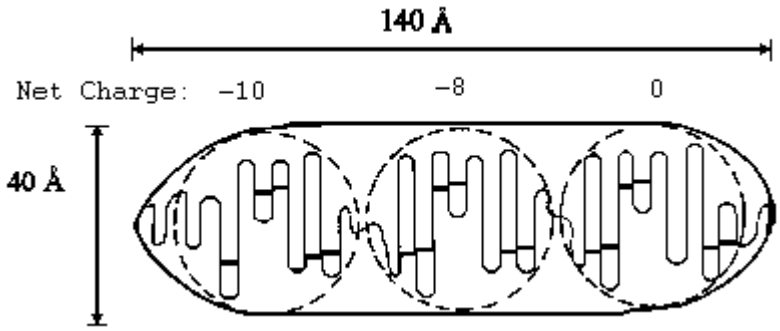


Figure 9 : Structure of albumin in solution

ALBUMIN METABOLISM

Serum albumin concentration depends on the rate of its production and degradation and also its distribution in the intravascular and extravascular compartments. The total body albumin pool is about 3.5-5g/kg bodyweight. 42% of this is in the plasma compartment and the rest is in extravascular compartment. A part of this is tissue bound and hence out of circulation. There is a daily loss of 120-145g of albumin into the extravascular space, most of which is brought back into circulation by lymphatic drainage. There is an intestinal loss of about 1g/day and after digestion, there is reabsorption of amino acids and peptides. About 70kg of albumin passes through the kidneys everyday, of which a few grams are filtered through the glomerulus. This is almost completely reabsorbed and finally only 10-20mg of albumin is lost through urine everyday.

EXTRAVASCULAR POOL OF ALBUMIN

- Skin, though comprises only 18% of body weight, has 41% of total extravascular albumin.
- Muscle, which forms 45.5% of body weight, contains 40% of extravascular albumin.

- Gut and liver, which constitute 2.8% and 4.1% of body weight respectively, have 7% and 3% of extravascular albumin respectively.
- Subcutaneous tissue, which forms 8% of body weight, contains 9% of albumin.
- Extravascular pool has exchangeable and remote components
- Albumin escapes into extravascular compartment across capillaries
- Half of this occurs through continuous capillaries facilitated by an active transport mechanism
- Rate of escape depends on the permeability of the vessel wall and the hydrostatic and oncotic pressures on both sides of the wall (Starling's law)
- Albumin binds to the the surface receptor- ALBONDIN
- Albondin is present in most of the capillary beds except in the brain
- Bound albumin enters the vesicles in the endothelial cell and gets released on the interstitial side within 15seconds.
- Rate of transfer increases on addition of long chain fatty acids, with cationisation and with glycosylation[43].

SYNTHESIS

- ✓ Synthesised only by liver in humans
- ✓ Liver can increase the synthesis to 2-2.7 times the normal
- ✓ Secreted into portal circulation soon after manufacture
- ✓ In healthy young adult, rate of synthesis is 194mg/kg/day, about 12-25g/day
- ✓ Albumin synthesis requires a suitable nutritional, hormonal and osmotic environment
- ✓ Colloid osmotic pressure of the interstitial fluid surrounding the hepatocyte is the most important regulator of albumin synthesis
- ✓ Requirements for synthesis :
    - mRNA for translation
    - adequate supply of amino acids, activated by binding to tRNA
    - ribosomal machinery for assembly
    - energy as ATP or/and GTP

Factors causing reduced albumin synthesis : (Table 4)

Decreased gene transcription	▪ Trauma, sepsis ▪ Hepatic disease ▪ Diabetes ▪ Decreased growth hormone ▪ Decreased steroids
Ribosome disaggregation	Decreased nutritional intake

A decrease in gene transcription results in a decrease in mRNA concentration. This occurs in acute phase reactions where it is mediated by cytokines mainly interleukin-6 and tumour necrosis factor α. Rate of albumin synthesis is controlled by the mRNA concentration available for action on ribosomes. mRNA content is decreased in trauma and disease processes. Decreased gene transcription is also seen in hepatoma cells and in hepatocytes damaged with carbon tetrachloride.

Albumin synthesis requires insulin. Decreased synthesis in diabetes improves with insulin supplementation. Growth hormone stimulates gene transcription in hepatocytes[44].

Steroids have a complex role on albumin synthesis. Combination of steroids with insulin or aminoacids cause increase synthesis. But steroids also increase albumin catabolism.

Fasting reduces albumin production and protein restriction decreases it all the more. In the early phase of protein deprivation, the rapid disintegration of free and bound polysomes can be reversed by refeeding with aminoacids especially tryptophan and ornithine. Tryptophan is incorporated into albumin, but ornithine is not. Prolonged protein deprivation causes a 50-60% decrease in the concentration as well as activity of mRNA. Energy is more important than amino acids under normal circumstances for polysome aggregation. Reduced synthesis in starvation is found to correct with glucose refeeding alone which causes polysome reaggregation[45].

DEGRADATION

- ✓ Total daily albumin degradation is about 0.2g/kg/day
- ✓ This constitutes about 5% of daily whole body protein turnover

Most of the organs in the body are involved in the breakdown of albumin. 40-60% of albumin is broken down by muscles and skin. 10% leaks into gastrointestinal tract via stomach wall. Kidneys are responsible for another 10%. Though the liver has a high rate of metabolism, it degrades less than 15%.

Endothelial surface membrane scavenger receptors, gp18 and gp30, bind to altered, denatured albumin. This is taken up by the endocytotic vesicles which fuse with the lysosomes in the endothelial cells. Chemical modification of the circulating albumin is a signal for receptor-linked lysosomal degradation.

Chemical modification may also prevent degradation. Molecule is protected from breakdown by the binding of long chain fatty acids to albumin. In hypoalbuminemia, the ratio of long chain fatty acid to albumin increases and breakdown is suppressed.

The final products of degradation are free amino acids. These join the amino acid pools inside the cells and in the plasma.

FUNCTIONS OF ALBUMIN

(i) MAINTAINING ONCOTIC PRESSURE

Albumin has higher concentration in plasma than other plasma proteins. It has a molecular weight of 66.5kDa. Though this is less than the average weight of globulin (147kDa), albumin has great osmotic impact. Because of the high molecular weight and plasma concentration, in health, albumin contributes to 80% of the normal oncotic pressure. 60% of this is due to the direct osmotic effect. Negative charge of the molecule is responsible for the remaining 40%. This negative charge is responsible for the attractive force that causes intravascular retention of positively charged solute particles (Gibbs- Donnan effect).

Albumin, because of its large extravascular pool, water solubility and negative charge, has a major role in the regulation of tissue fluid distribution.

(ii) BINDING OF SUBSTANCES

Albumin has a structure that can incorporate several different substances. Also the structure is flexible and bound substances can be buried within its structure. The charge of the binding substance and the strength of binding have no correlation.

- Substances that bind most strongly to albumin : medium-sized hydrophobic organic anions – long chain fatty acids, bilirubin, haematin
- Substances that bind specifically but with less affinity : Ascorbate, tryptophan
- Chirality of the substance also determines the strength of binding
- Divalent cations like calcium and magnesium bind, but monovalent cations do not
- Basic drugs tend to bind to albumin
- Endogenous substances that bind to albumin : Bile acids, eicosanoids, copper, zinc, folate, aquacobalamin
- Secondary or tertiary carrier for substances with specific binding proteins :

  Steroids, vitamin D, thyroxine

Drug Binding

Binding of the drug to albumin affects its delivery to tissues and also its metabolism and elimination. This also determines the free serum concentration of the drug. Highly bound drugs have less concentration of their free form in serum. Drug- albumin interactions are responsible for the wide interindividual variations in response to drugs. Factors like age, temperature, pH and ionic strength influence the drug-albumin interactions. These alter the number of functional binding sites and the competition between drugs for binding sites. Endogenous substances or other drugs may displace the drug from its binding site and thereby the distribution, pharmacological action, metabolism and excretion of the displaced drug are altered.

Binding sites on albumin are broadly classified into site I and site II.

Site I : Along the long loop of subdomain IIa extending into the shorter loop

Drugs binding to this site: Salicylates, warfarin, phenylbutazone, Indomethacin, digitoxin, furosemide, Phenytoin, chlorpropamide, pencillins

Dyes like sulfobromophthalein, iophenoxate, Methyl red, Evans blue, bromocresol green

Bilirubin

Site II : Hydrophobic pocket of residues in subdomain IIIa

Substances binding to this site : L-tryptophan, thyroxine, chloride, Medium- chain fatty acids, Diazepam, benzodiazepines, Ibuprofen, naproxen, clofibrate

(iii) METABOLIC FUNCTION

Albumin causes the inactivation of certain compounds like disulfiram, penem group of antibiotics etc. Because of the avidity of binding, albumin has a role in the metabolism of substances like lipids and eicosanoids. Albumin stabilizes eicosanoids like prostaglandin I_2 and thromboxane A_2. It also releases arachidonic acid from macrophages and favours lipooxygenase activity over that of cyclooxygenase.

Pencillin allergy is due to irreversible coupling of pencilloyl groups to lysine groups in site 1. This causes production of antibodies to drug-albumin complex.

(iv) ACID-BASE FUNCTION

Albumin acts as an effective buffer by its relative abundance in plasma as well as the presence of charged residues on the molecule. At physiological pH, albumin contributes to half the normal anion gap with a net negative charge of 19. A decrease in serum albumin of 1g/dl increases the standard bicarbonate by 3.4mmol/L thereby reducing the anion gap by 3mmol/litre.

(v) ANTIOXIDANT FUNCTION

Albumin has antioxidant potential under physiological conditions. It scavenges the free radicals which are involved in the pathogenesis of various diseases. The production of oxygen free radicals by activated polymorphonuclear leucocytes from the enzyme myeloperoxidase is also inhibited by physiological solutions of human albumin. This action is due to the sulfhydryl groups on albumin.

(vi)MAINTAINING MICROVASCULAR INTEGRITY

Albumin controls the stress-induced increase in capillary permeability. This action is brought about by the endothelial cells which alter the permeability of the capillary membrane by altering the nature and distribution of glycoproteins in the vessel wall. This may be due to

the negative charge of the molecule or the reduction in the size of channels by the albumin molecule. Albumin prevents the apoptosis of endothelial cells, the peak action being at physiological concentrations.

Albumin slows the onset and enhances the vasodilatory response to nitric oxide. Nitric oxide by binding to the sulfhydryl groups of albumin, forms stable S-nitrosothiol group which is not rapidly degraded. Thus albumin plays a role in the regulation of vasodilatory tone of vessels.

(vii)ANTICOAGULANT EFFECTS

Has Heparin-like action due to resemblance in the structure of molecules with plenty of negatively charged groups. Heparin exerts its anticoagulant effect by the binding of negatively charged sulphate groups to the positively charged groups on antithrombin III. Albumin enhances the neutralization of factor Xa by antithrombin III. This explains the negative correlation between albumin concentration and heparin requirement in patients on hemodialysis. This might also explain the hypercoagulable state occurring in nephrotic syndrome. Albumin also exerts an inhibitory effect on platelet aggregation both dependent and independent of the cyclooxygenase system.

ANALBUMINEMIA

Albumin has large number of variants, about 100, based on the electrophoretic mobility. Only one variant, which has high affinity for thyroxine, is known to affect the function of albumin, thereby causing Familial Dysalbuminemic Hyperthyroidism[46].

Analbuminemia has been defined as serum albumin concentration of less than 1g/litre. There is a small amount of albumin in circulation which is adequate under normal conditions. But in times of stress, when the requirement shoots up, features manifest. It is a rare condition which may be sporadic or familial. If familial, it has autosomal recessive inheritance. Albumin gene is present, but genetic mutations produce effects which prevent translation.

Cases usually present in adulthood. The features are:

- Peripheral oedema
- Lipodystrophy causing lower limb obesity
- Fatigue
- Hyperlipidemia without atherosclerosis
- Reduced oncotic pressure

- Decrease in arterial pressure causing increased rennin and aldosterone concentrations.

Body tries to compensate for the low serum albumin by slowing the rate of degradation.

ALBUMIN IN CRITICAL ILLNESS

Critical illness brings about changes in the distribution and metabolism of albumin.

CHANGES IN DISTRIBUTION

There is alteration in the distribution of albumin between the intravascular and extravascular compartments. The underlying pathology is an increased capillary leakage. There occurs endothelial dysfunction, causing capillary leakage and loss of proteins, inflammatory cells and large volumes of fluid into the interstitial space. The mediators of this process are :

- Endotoxins of gram-negative bacteria
- Cytokines – TNF-α and IL-6
- Leukotrienes and prostaglandins
- Complement components- C3a and C5a

- Vasoactive peptides like bradykinin and histamine
- Chemokines like macrophage inflammatory protein 1α

This altered distribution is predominantly seen in sepsis and after major surgical stress. The transcapillary escape rate increases upto 300% in septic shock and by 100% after cardiac surgery. In sepsis, this improves with appropriate treatment. When albumin moves out of the vascular compartment, there is a resultant increase in lymphatic flow intravascularly. There is a 30% reduction in the total circulating and total exchangeable albumin pools following major surgery. This is mainly due to the sequestration of albumin in non-exchangeable sites like wounds, intestine and extra-abdominal sites.

CHANGES IN METABOLISM

There occurs alteration in the synthesis and degradation of albumin resulting in a dramatic decrease in serum albumin concentration even early in the course of a critical illness[47].

Synthesis

In trauma, inflammation or sepsis, the acute phase response involves an increase in the gene transcription rate of positive acute phase proteins like C-reactive protein and a decreased rate of albumin synthesis.

The decreased synthesis is due to reduced gene transcription which is mediated by IL-6 and TNFα. A sustained inflammatory response results in prolonged inhibition of albumin synthesis.

Catabolism

The degradation rate is mass dependent. So when serum albumin concentration decreases, degradation rate also decreases. But in increased transcapillary escape of albumin, there is an increase in degradation rate. Vascular endothelium is thought to play a major role in the degradation of albumin. More of tissue exposure in the presence of increased capillary permeability may increase catabolism. But in myxoedema, though there is an expansion in the extravascular pool of albumin, there is decreased degradation which could be due to the tissue exposure and trapping which protects the albumin from degradation.

There is a huge difference in the kinetics of intravenous albumin between critically ill and healthy subjects. The point of interest in this aspect is that increasing the intravascular albumin concentration using exogenous albumin may be beneficial in critical illness.

Oncotic pressure is low in patients who are critically ill and this may be associated with increased mortality and morbidity. There are arguments that supplementation of albumin can increase the oncotic

pressure and thereby avoid life threatening complications like pulmonary oedema. At the same time, there are studies which suggest that pulmonary dysfunction in sepsis is independent of oncotic pressure.

Drug- albumin interactions are altered in critical illnesses. In renal failure, there is accelerated loss of albumin through damaged glomeruli. The binding of drugs to albumin is also altered in renal failure, probably by changes in pH and the accumulation of compounds which compete with drugs for the binding sites. This results in increased free fraction of drugs causing enhanced drug effect in renal failure. Thus it becomes necessary that the free serum levels of drugs should be monitored in renal failure in order to avoid toxicity.

PROGNOSTIC VALUE OF SERUM ALBUMIN

Serum albumin acts as an independent predictor of mortality in various clinical settings. Serum levels of albumin may also serve as a marker of subclinical disease in elderly patients. Studies in hospitalized patients have revealed that low serum concentration of albumin is associated with prolonged hospital stay, more complications and higher mortality. It also correlates with prolonged stay in intensive care unit, more ventilatory requirement and increased rate of infections. The daily trend of serum albumin may be used as a guide to predict the weaning

capability of patients on mechanical ventilation[48]. Serum albumin values at 24-48hours of ICU admission were found to be as good as APACHE II score in predicting mortality. APACHE III system takes serum albumin value into consideration and has better predictive value for mortality in critical illnesses[49]. Serum albumin, though considered a measure of nutrition, is not a reliable marker of nutritional status in critically ill.

INTRAVENOUS ALBUMIN THERAPY

There is no proven benefit for intravenous albumin over other colloids in volume replacement in critically ill patients.

Serum albumin has a beneficial role in burns patients. In the first 24 hours, there is a gross increase in capillary permeability with marked transcapillary fluid shifts. Beyond 24 hours, intravenous albumin promotes reabsorption of plasma. According to the Guidelines Of the Consensus Conference in Paris[50], burns less than 15% of body surface area do not require albumin. Those involving more than 50% surface area require albumin right from the start of treatment. For those in between, albumin supplementation can wait 24 hours.

Albumin therapy is also beneficial in cirrhotic patients with ascites who require paracentesis. Postparacentesis circulatory dysfunction which is the increased plasma renin activity 6 days after paracentesis is prevented by albumin therapy.

LIMITATIONS

- Injudicious use can cause fluid overload doe to plasma expansion.
- Myocardial depression probably due to binding of calcium ions.
- Allergic reactions- mostly to contaminants in solution or polymers formed during storage.
- Viral transmission though unlikely due to prolonged heat treatment during preparation[51], there is theoretical risk of Creutzfield- Jakob disease.
- Expensive

More of research and interventional studies are required and several controversies to be cleared before albumin therapy becomes an accepted treatment modality to reduce mortality in critically ill patients.

MATERIALS & METHODS

This observational study was conducted in Coimbatore Medical College over a period of six months from December 2013 to May 2014. It was approved by the Ethical Committee, Coimbatore Medical College.

The study population comprised of 100 patients who got admitted in medical wards with first ever acute ischemic stroke within 72 hours of onset of symptoms. The patients were included in the study after getting informed consent either from the patient himself or from the legal guardian.

Study design : Prospective study

Exclusion criteria :

- Patients presenting >72hrs after onset of symptoms
- Previous history of stroke
- Hemorrhagic stroke
- Stroke due to tuberculoma, tumour or trauma
- Subarachnoid hemorrhage
- Patients with known renal or hepatic disease
- Patients with fever & infections

Cases were defined as per WHO definition of stroke. Hypertension was diagnosed if there were records documenting the same or when at least 2 readings of blood pressure were ≥140mmHg systolic or ≥90mmHg diastolic after the acute phase of stroke. Coronary artery disease was diagnosed in the presence of ECG changes or previous records. Patient was considered a smoker if he had a history of smoking in the past 5 years.

About 212 consecutive patients who were admitted with first ever attack of stroke were screened to get the study population of 100. Patients first underwent a CT scan of the Brain to rule out hemorrhagic stroke or any obvious mass lesions. A detailed history was elicited followed by general examination, an elaborate CNS examination and relevant examination of other systems. Stroke severity was graded using the Scandinavian Stroke Scale. Blood and urine investigations were done including complete hemogram, blood sugar, renal function test, liver function test with serum proteins, lipid profile and urine routine examination.ECG was also taken. Cases who met the exclusion criteria were excluded. Patients received treatment as per Institution guidelines. Patients were followed up and on the 7^{th} day after onset of stroke, their functional status was assessed using Modified Rankin Scale either in person if patient still in hospital or over the phone if discharged.

Serum albumin levels were measured using Bromocresol Green.

The obtained data was entered into a Microsoft Excel spreadsheet and analysed statistically using SPSS (Statistical Package for Social Sciences) (version 18). The significance of association was tested using Chi-square test and correlation was measured by Pearson Correlation Coefficient. The statistical analysis was done to find out the significance of association, if any, between serum albumin value at admission and the severity of stroke at admission as well as the functional outcome at 7 days and also to find out the correlation between these variables.

Scandinavian Stroke Scale

Patient name:
Rater name:
Date:

ASSESSMENT	SCORE
Consciousness	
Fully conscious	6
Somnolent, but can be awakened to full consciousness	4
Reacts to verbal command but is not fully conscious	2
Eye movement	
No gaze palsy	4
Gaze palsy present	2
Conjugate eye deviation	0
Arm, motor power	
Raises arm with normal strength	6
Raises arm with reduced strength	5
Raises arm with flexion in elbow	4
Can move but not against gravity	2
Paralysis	0
Hand, motor power	
Normal strength	6
Reduced strength in full range	4
Some movement, fingertips do not reach palm	2
Paralysis	0
Leg, motor power	
Normal strength	6
Raises straight leg with reduced strength	5
Raises leg with flexion of knee	4
Can move but not against gravity	2
Paralysis	0
Orientation	
Correct for time, place and person	6
Two of these	4
One of these	2
Completely disorientated	0
Speech	
No aphasia	10
Limited vocabulary or incoherent speech	6
More than yes/no but no longer sentences	3
Only yes/no or less	0
Facial palsy	
None / dubious	2
Present	0
Gait	
Walks 5m without aids	12
Walks with aids	9
Walks with the help of another person	6
Sits without support	3
Bedridden / wheelchair	0
SCORE (Maximal score is 58)	

Motor power is only assessed on the affected side.

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

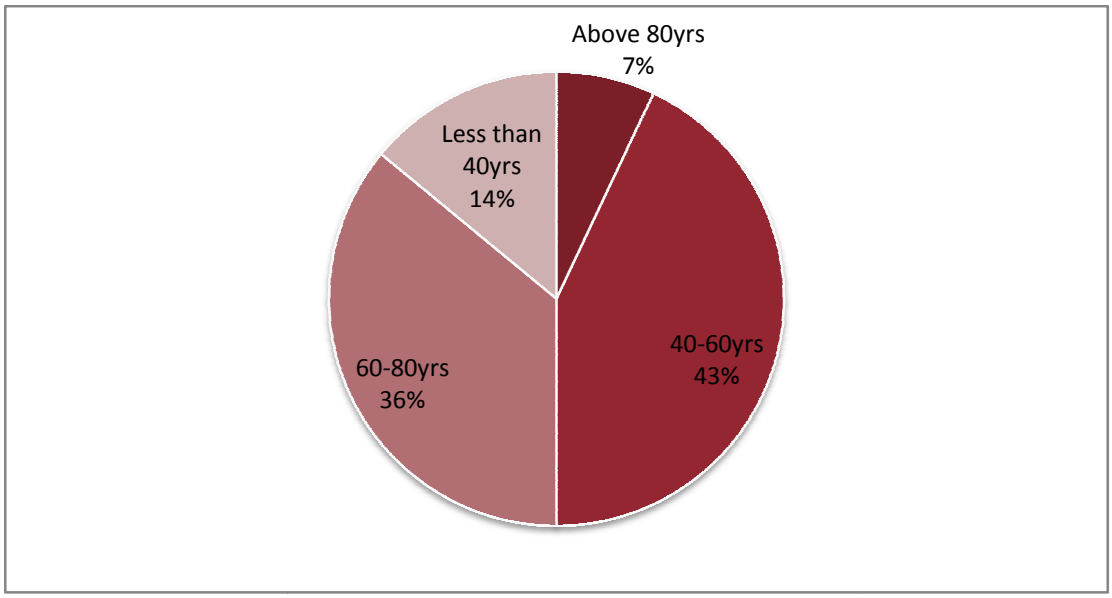
OBSERVATIONS AND RESULTS

AGE DISTRIBUTION

Table 5 :

AGE GROUP	FREQUENCY
Less than 40 years	14
40- 60 years	43
60- 80 years	36
Above 80 years	7
Total	100

Chart 3:



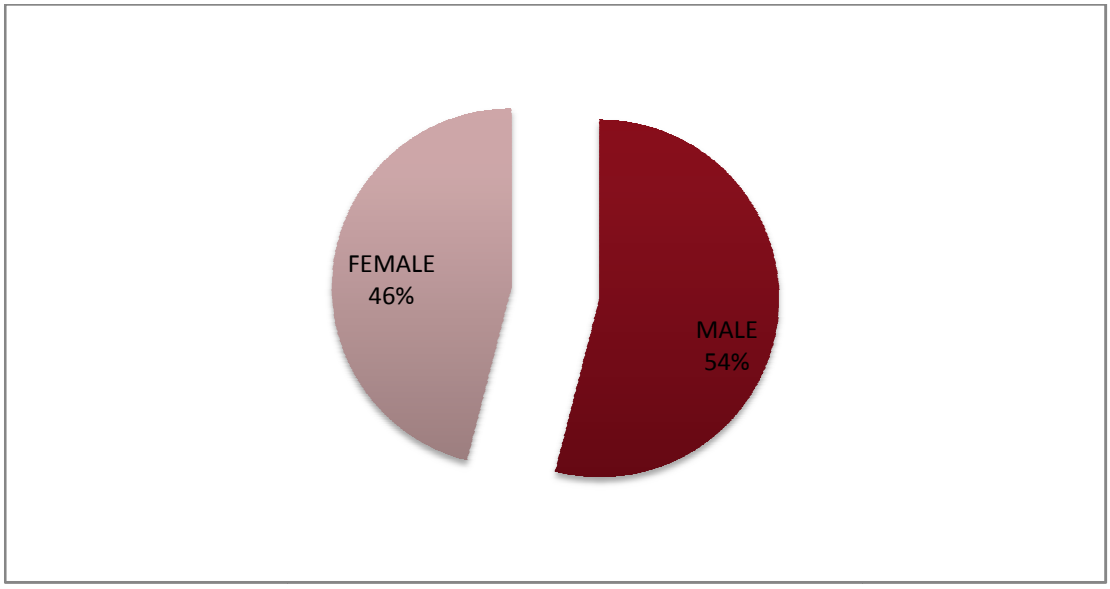
Of the 100 patients included in the study, majority were in the 40-60yrs age group. Mean age of the study group was 58.44 ± 14.42yrs.

SEX DISTRIBUTION

Table 6:

GENDER	FREQUENCY
MALE	54
FEMALE	46
TOTAL	100

Chart 4:



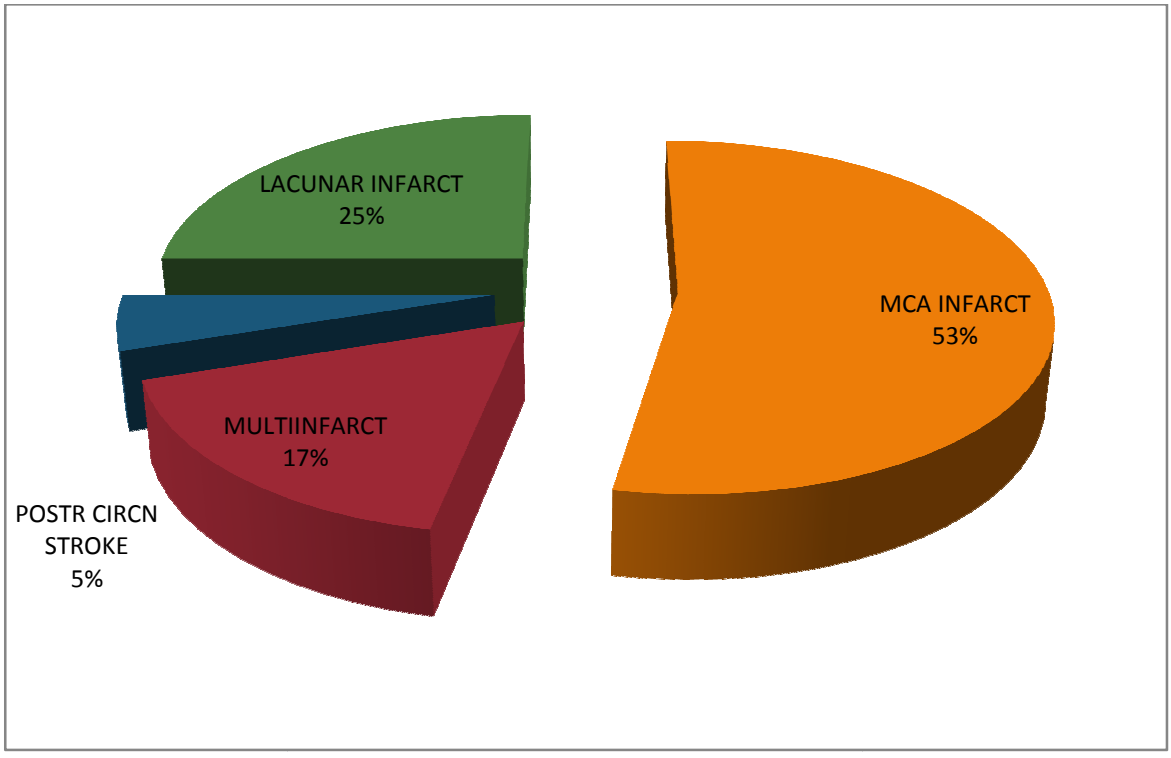
The study group had a near equal proportion of males and females with slight male predominance.

FREQUENCY OF LESIONS IN CT BRAIN

Table 7:

LESION	FREQUENCY
MCA INFARCT	53
MULTIINFARCT	17
POSTERIOR CIRCULATION STROKE	5
LACUNAR STROKE	25
TOTAL	100

Chart 5 :

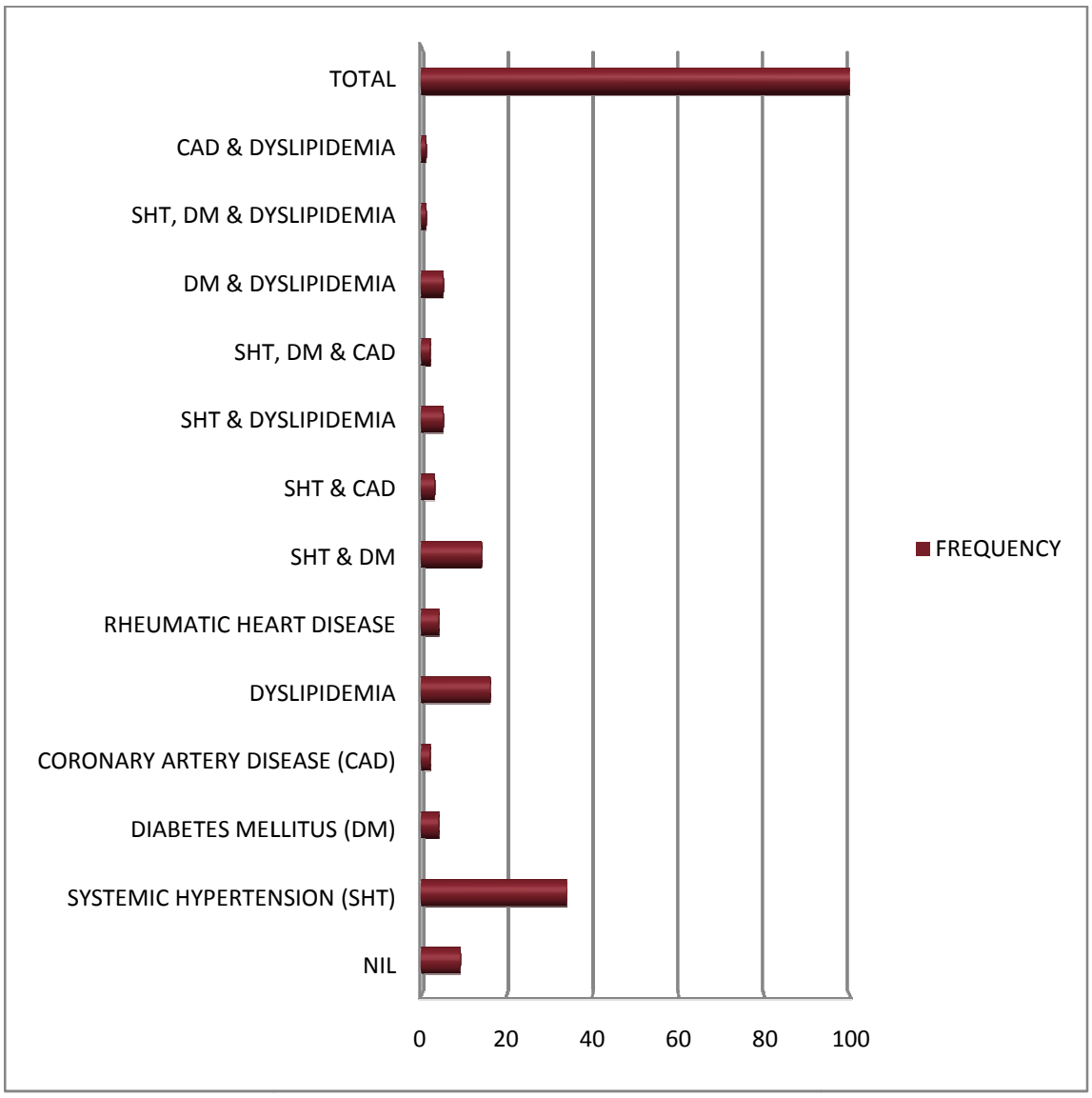


DISTRIBUTION OF COMORBID CONDITIONS IN THE STUDY POPULATION

Table 8:

COMORBIDITY	FREQUENCY
NIL	9
SYSTEMIC HYPERTENSION (SHT)	34
DIABETES MELLITUS (DM)	4
CORONARY ARTERY DISEASE (CAD)	2
DYSLIPIDEMIA	16
RHEUMATIC HEART DISEASE	4
SHT & DM	14
SHT & CAD	3
SHT & DYSLIPIDEMIA	5
SHT, DM & CAD	2
DM & DYSLIPIDEMIA	5
SHT, DM & DYSLIPIDEMIA	1
CAD & DYSLIPIDEMIA	1
TOTAL	100

Chart 6:



Systemic hypertension was found to be the most frequently associated comorbidity followed by dyslipidemia and a combination of hypertension and diabetes mellitus.

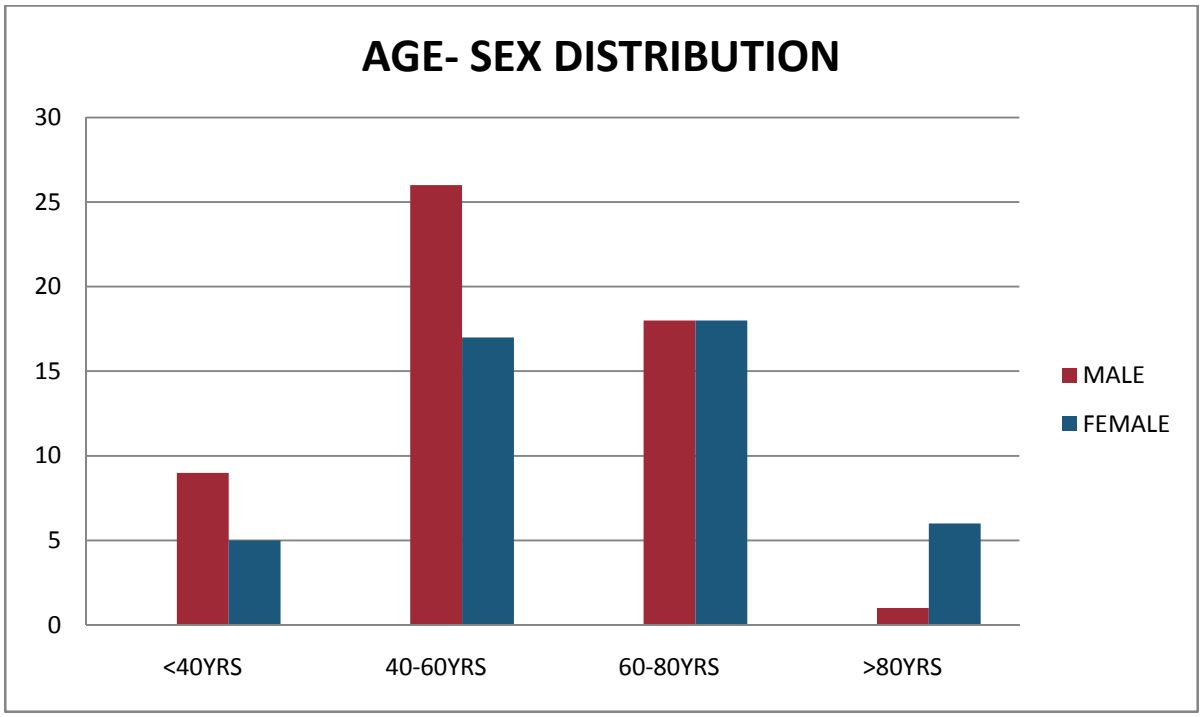
AGE – SEX DISTRIBUTION IN THE STUDY POPULATION

Table 9:

Crosstab

			AGE				
			Less than 40 years	40 - 60 years	60 - 80 years	Above 80 years	Total
SEX	Male	Count	9	26	18	1	54
		% within SEX	16.7%	48.1%	33.3%	1.9%	100.0%
		% within AGE	64.3%	60.5%	50.0%	14.3%	54.0%
	Female	Count	5	17	18	6	46
		% within SEX	10.9%	37.0%	39.1%	13.0%	100.0%
		% within AGE	35.7%	39.5%	50.0%	85.7%	46.0%
Total		Count	14	43	36	7	100
		% within SEX	14.0%	43.0%	36.0%	7.0%	100.0%
		% within AGE	100.0%	100.0%	100.0%	100.0%	100.0%

Chart 7:



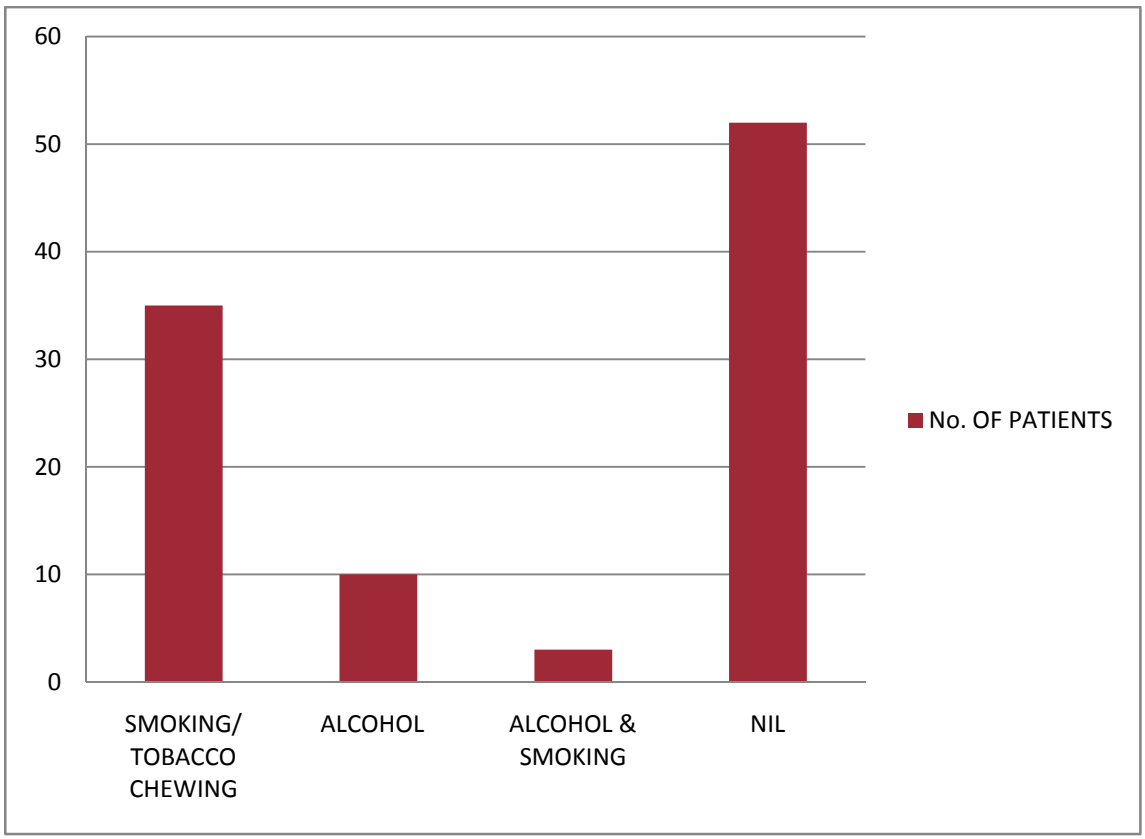
The mean age of males was 55 and that of females was 62.

PREVALENCE OF ADDICTIONS IN THE STUDY POPULATION

Table 10:

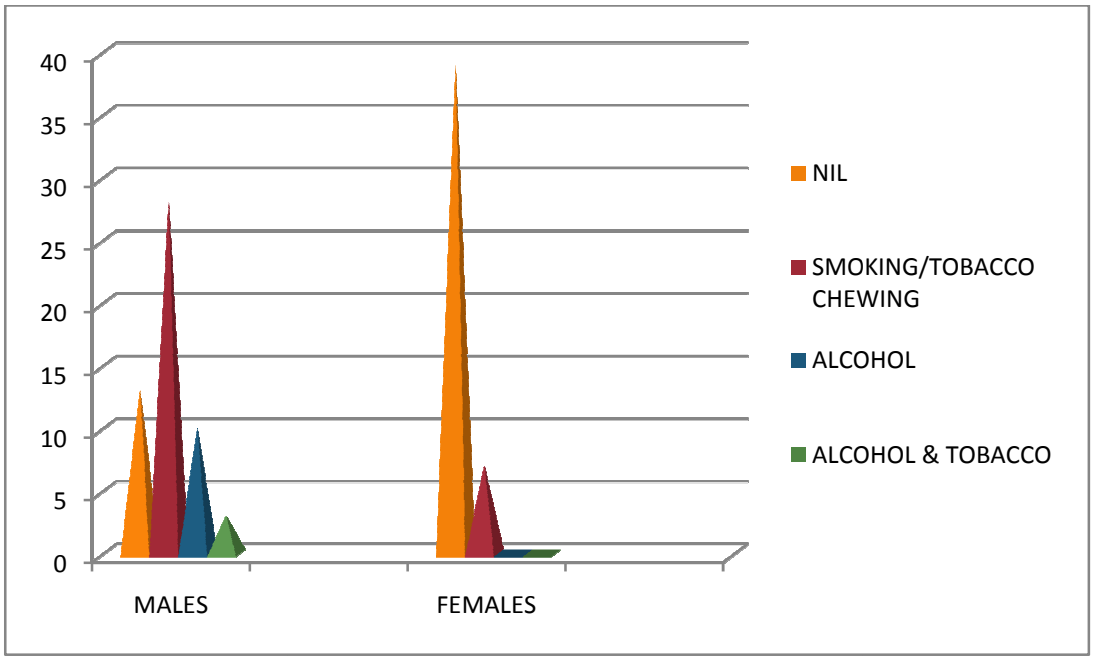
ADDICTION	FREQUENCY
SMOKING/ TOBACCO CHEWING	35
ALCOHOL	10
ALCOHOL/TOBACCO	3
NIL	52
TOTAL	100

Chart 8:



FREQUENCY OF ADDICTIONS IN MALES AND FEMALES

Chart 9:



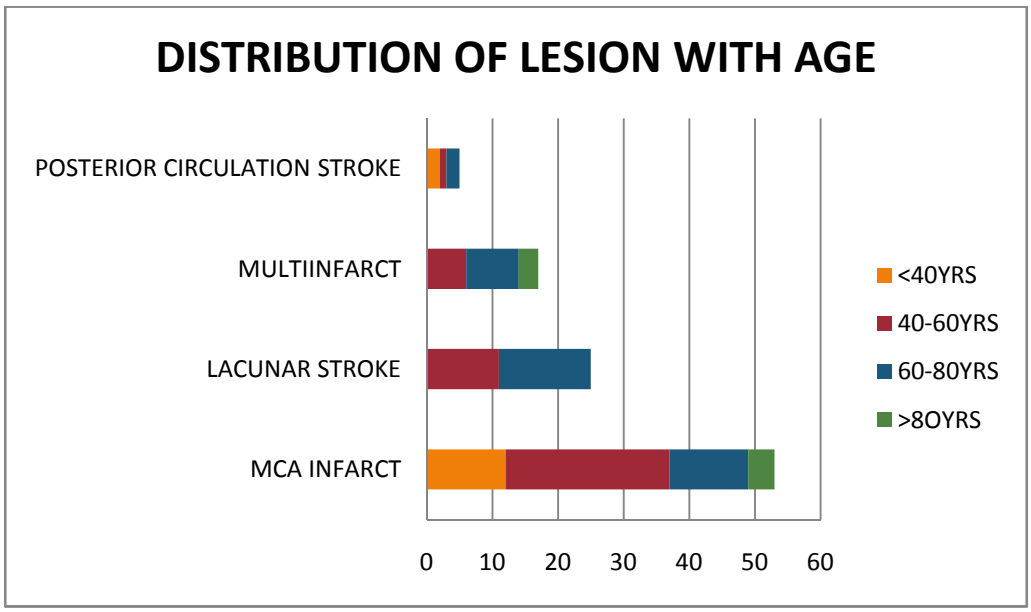
ASSOCIATION OF LESIONS WITH AGE

Table 11:

Crosstab

			AGE				
			Less than 40 years	40 - 60 years	60 - 80 years	Above 80 years	Total
LESION	MCA Infarct	Count	12	25	12	4	53
		% within LESION	22.6%	47.2%	22.6%	7.5%	100.0%
		% within AGE	85.7%	58.1%	33.3%	57.1%	53.0%
	Multi-infarct	Count	0	6	8	3	17
		% within LESION	.0%	35.3%	47.1%	17.6%	100.0%
		% within AGE	.0%	14.0%	22.2%	42.9%	17.0%
	PCA/ Posterior circulation stroke	Count	2	1	2	0	5
		% within LESION	40.0%	20.0%	40.0%	.0%	100.0%
		% within AGE	14.3%	2.3%	5.6%	.0%	5.0%
	Lacunar stroke	Count	0	11	14	0	25
		% within LESION	.0%	44.0%	56.0%	.0%	100.0%
		% within AGE	.0%	25.6%	38.9%	.0%	25.0%
Total		Count	14	43	36	7	100
		% within LESION	14.0%	43.0%	36.0%	7.0%	100.0%
		% within AGE	100.0%	100.0%	100.0%	100.0%	100.0%

Chart 10:



DISTRIBUTION OF COMORBIDITIES WITH AGE

Chart 11:

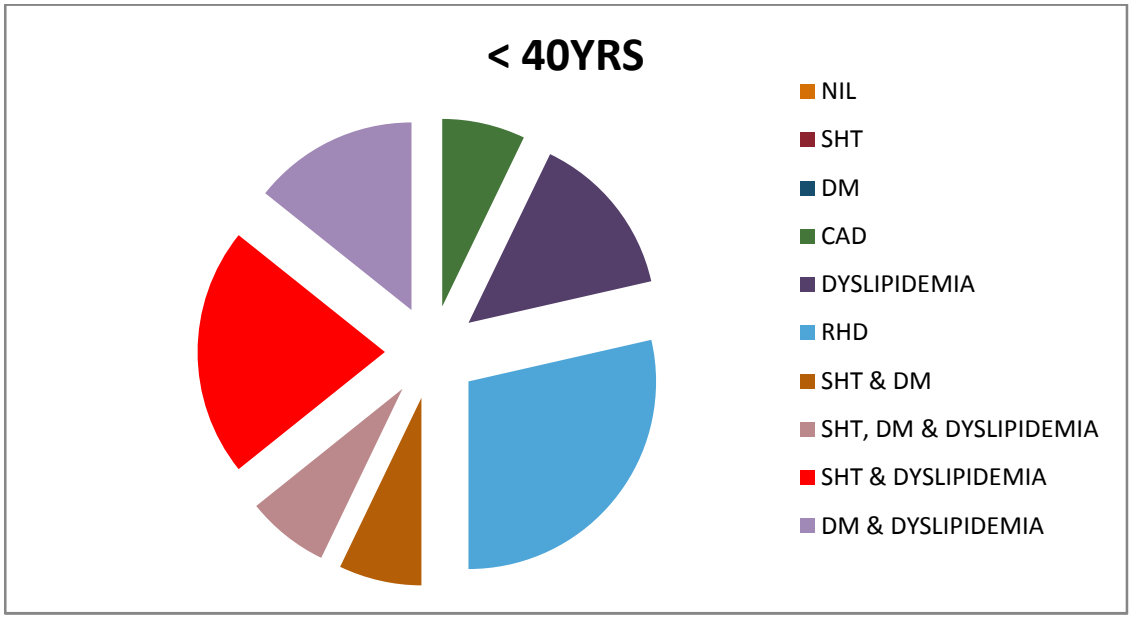


Chart 12:

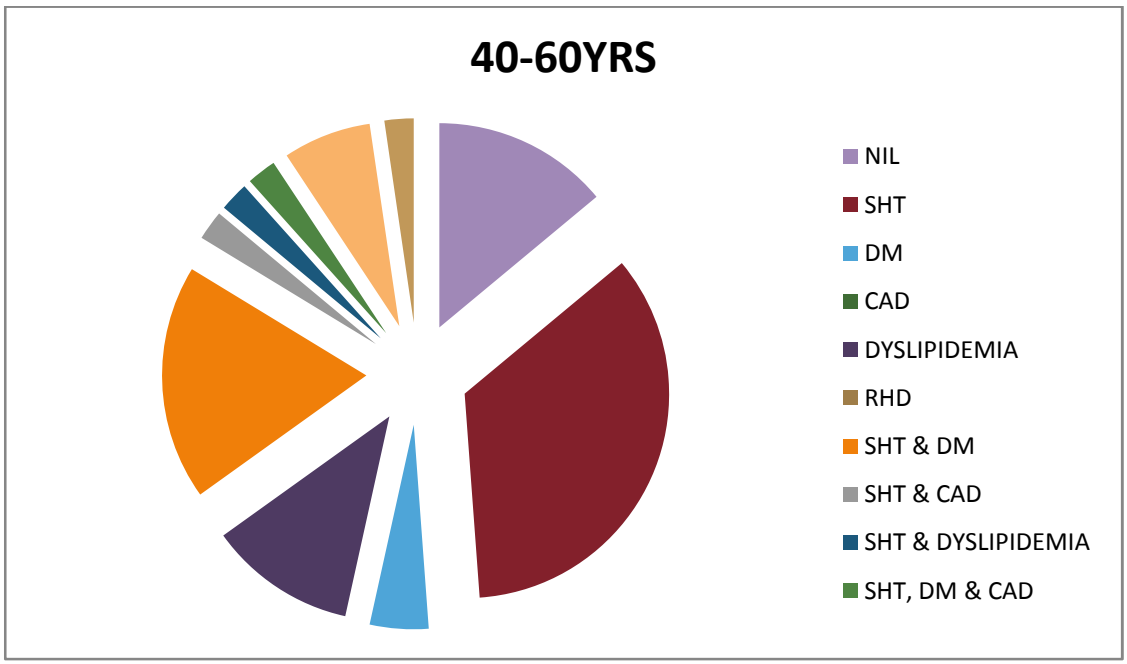


Chart 13 :

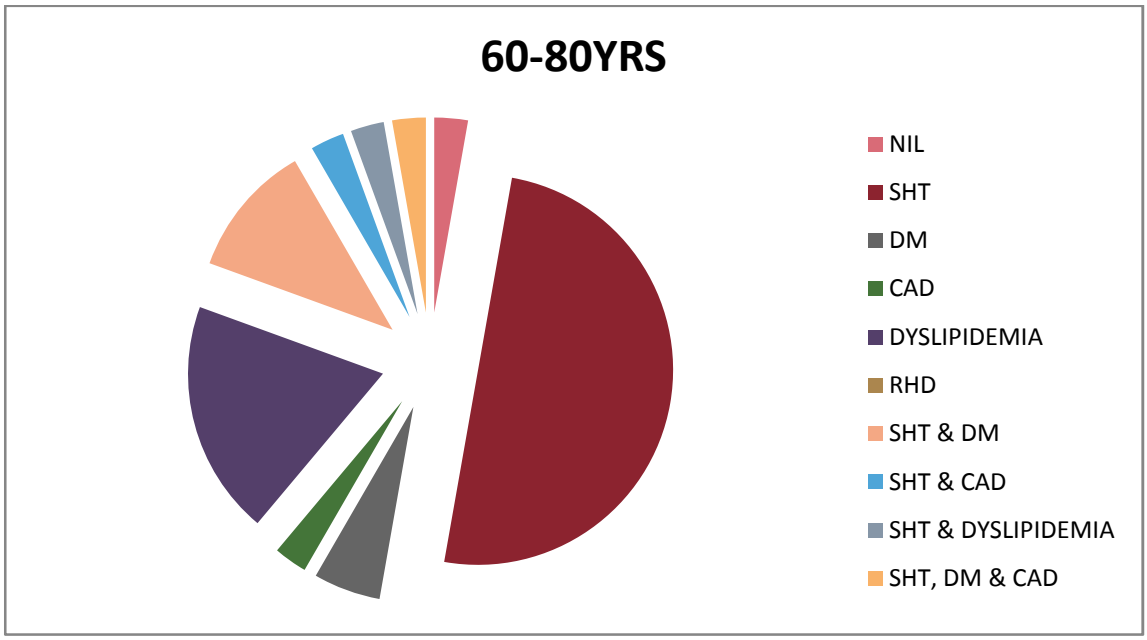
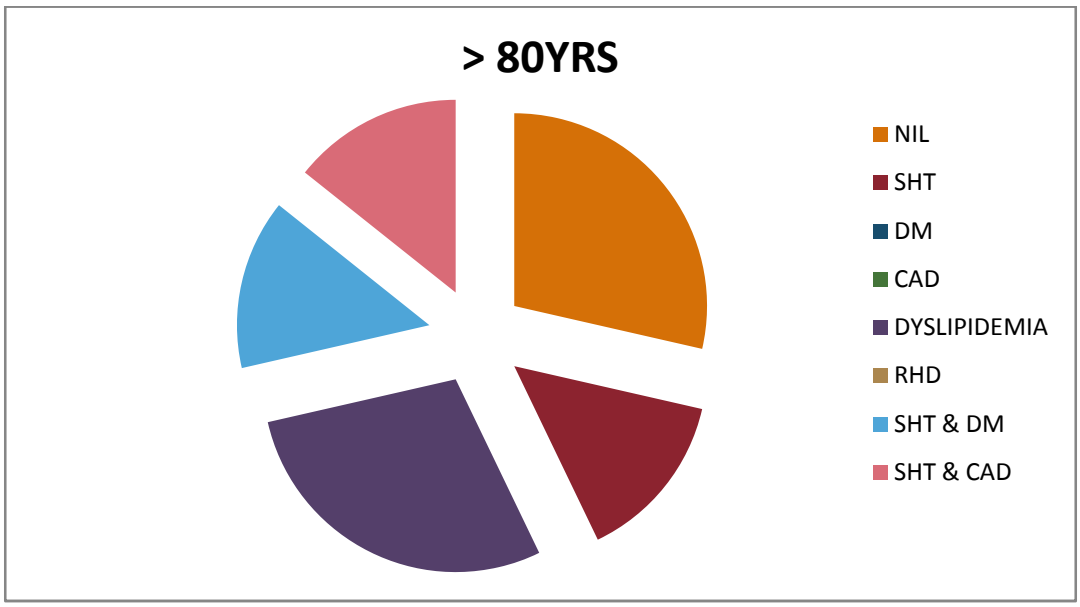


Chart 14 :



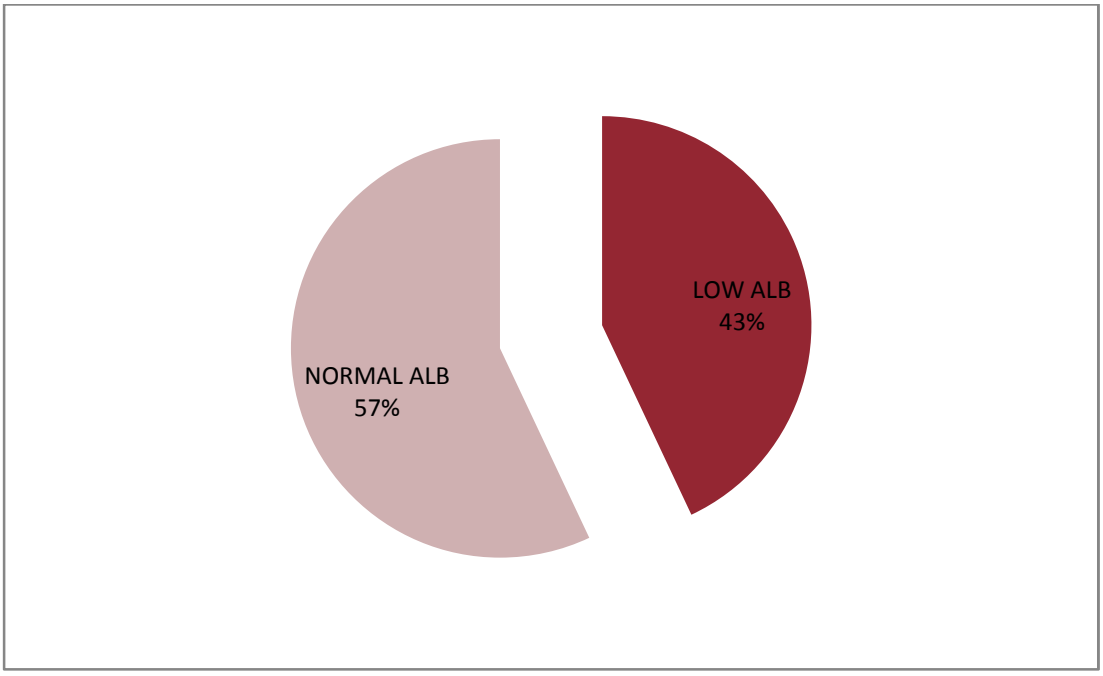
In young stroke (below the age of 40), rheumatic heart disease was the major associated comorbidity, whereas, in older age groups, hypertension predominates the picture.

DISTRIBUTION OF SERUM ALBUMIN IN THE STUDY POPULATION

Table 12:

SERUM ALBUMIN	FREQUENCY
NORMAL (3.5-5g/dl)	57
LOW (<3.5g/dl)	43
TOTAL	100

Chart 15 :



There was no gross difference in the number of stroke patients included in the study with regard to the levels of serum albumin.

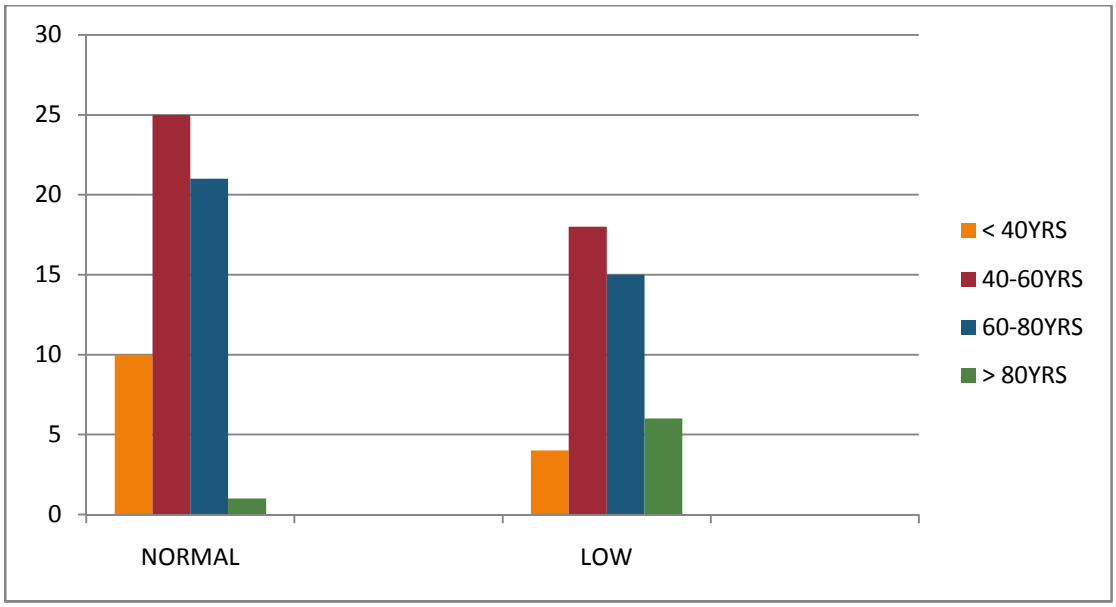
ASSOCIATION OF SERUM ALBUMIN WITH AGE

Table 13:

Crosstab

			AGE				
			Less than 40 years	40 - 60 years	60 - 80 years	Above 80 years	Total
S. ALBUM	Normal	Count	10	25	21	1	57
		% within S. ALBU	17.5%	43.9%	36.8%	1.8%	100.0%
		% within AGE	71.4%	58.1%	58.3%	14.3%	57.0%
	Low	Count	4	18	15	6	43
		% within S. ALBU	9.3%	41.9%	34.9%	14.0%	100.0%
		% within AGE	28.6%	41.9%	41.7%	85.7%	43.0%
Total		Count	14	43	36	7	100
		% within S. ALBU	14.0%	43.0%	36.0%	7.0%	100.0%
		% within AGE	100.0%	100.0%	100.0%	100.0%	100.0%

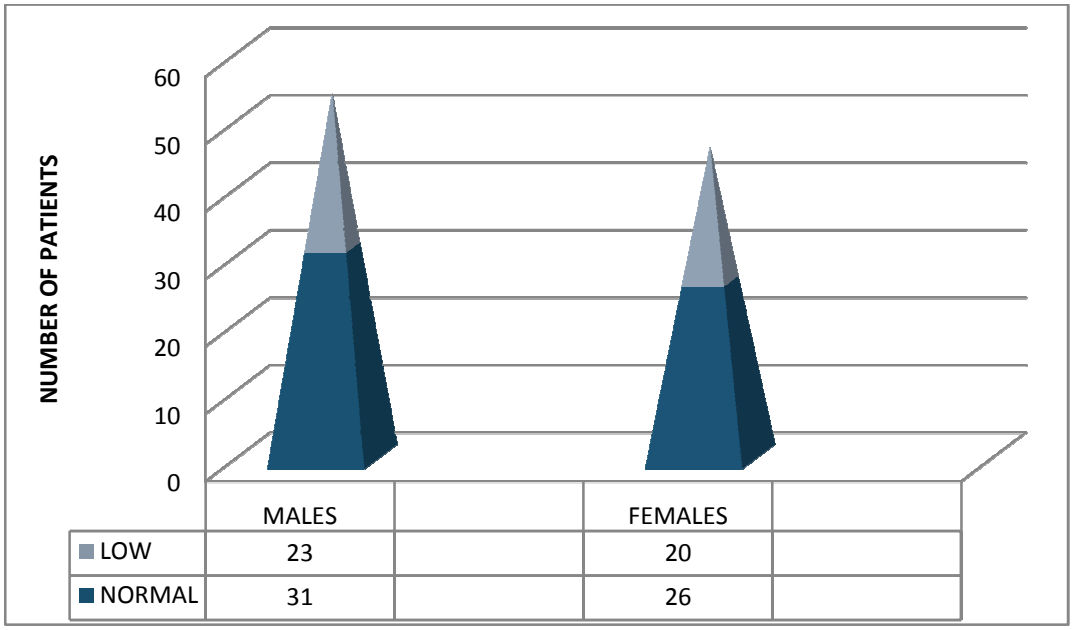
Chart 16:



The chi-square value of 6.45 for the association between age and serum albumin is not significant (p>0.05).

DISTRIBUTION OF SERUM ALBUMIN IN MALES AND FEMALES

Chart 17 :



In our study population, there was a fairly uniform distribution of serum albumin values with no gross difference in the number of males and females with normal and low albumin levels.

ASSOCIATION OF MRS SCORE AT 7DAYS WITH SEVERITY OF STROKE (SSS SCORE)

Table 14 :

SSS SCORE	SEVERITY	MRS SCORE				
		MILD	MODERATE	SEVERE	DEATH	TOTAL
	MILD	6	0	0	0	6
	MODERATE	17	12	7	0	36
	SEVERE	0	11	22	25	58
	TOTAL	23	23	29	25	100

In the above table, the chi-square value of 64.024 for the association between severity of the stroke as measured by the SSS score and the outcome as measured by the MRS score at 7 days is significant ($p < 0.05$). Hence we can infer that there is significant association between the severity of stroke at onset and the outcome at 7days.

ASSOCIATION OF SEVERITY OF STROKE (SSS SCORE) WITH SERUM ALBUMIN

Table 15 :

SSS SCORE	SEVERITY	SERUM ALBUMIN		
		NORMAL	LOW	TOTAL
	MILD	5	1	6
	MODERATE	28	8	36
	SEVERE	24	34	58
	TOTAL	57	43	100

In the above table, the chi-square value of 13.81 for the association between SSS score and serum albumin is significant ($p < 0.05$). This implies that there is significant association between the severity of stroke at presentation and the serum albumin value.

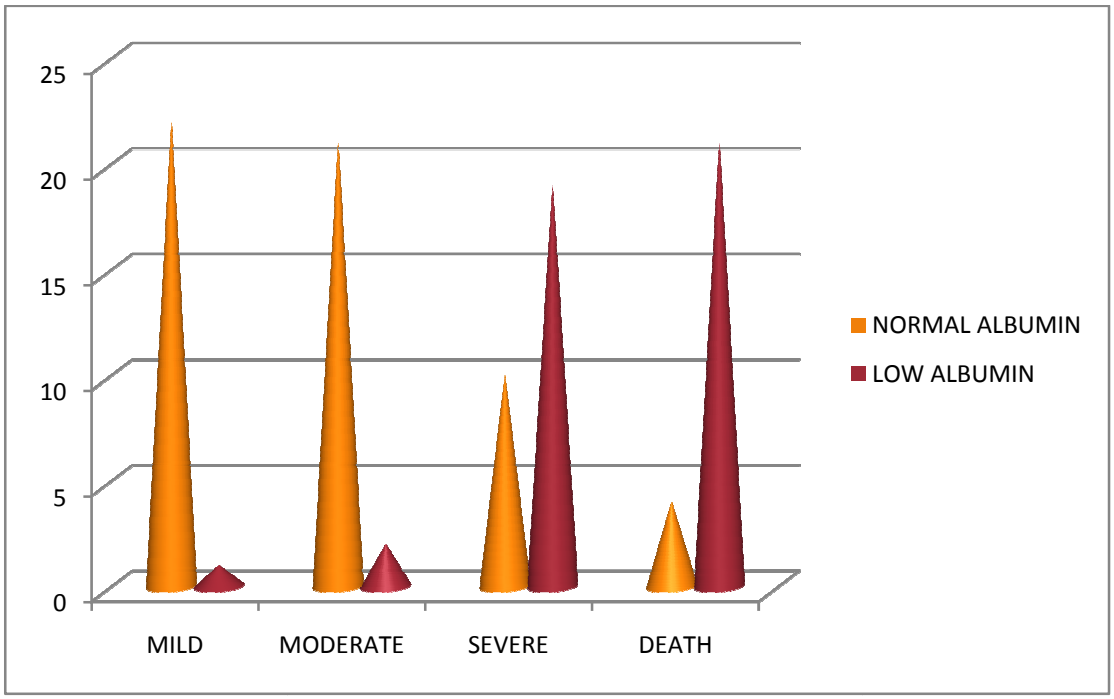
ASSOCIATION OF MRS SCORE AT 7 DAYS

WITH SERUM ALBUMIN

Table 16:

MRS SCORE	SEVERITY	SERUM ALBUMIN		
		NORMAL	LOW	TOTAL
	MILD	22	1	23
	MODERATE	21	2	23
	SEVERE	10	19	29
	DEATH	4	21	25
	TOTAL	57	43	100

Chart 18 :



The chi-square value for the association between MRS score and serum albumin, 48.21, is statistically significant ($p< 0.05$). this implies that the stroke outcome at 7days as measured by the Modified Rankin scale is significantly associated with the level of serum albumin at stroke onset. In our study population, 84% of deaths was in the group with low serum albumin values. Among the patients with low serum albumin values, 93% landed up with severe disability or death compared to 24.5% in patients with normal serum albumin. This reemphasizes the fact that serum albumin could be of prognostic significance in acute ischemic stroke.

CORRELATION BETWEEN SERUM ALBUMIN, GCS SCORE, SSS SCORE & MRS SCORE

Table 17:

Correlations

		GCS	S. ALBUMIN	SSS SCORE	MRS SCORE
GCS	Pearson Correlation	1	.612**	.859**	-.845**
	Sig. (2-tailed)		.000	.000	.000
	N	100	100	100	100
S. ALBUMIN	Pearson Correlation	.612**	1	.558**	-.700**
	Sig. (2-tailed)	.000		.000	.000
	N	100	100	100	100
SSS SCORE	Pearson Correlation	.859**	.558**	1	-.865**
	Sig. (2-tailed)	.000	.000		.000
	N	100	100	100	100
MRS SCORE	Pearson Correlation	-.845**	-.700**	-.865**	1
	Sig. (2-tailed)	.000	.000	.000	
	N	100	100	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

GCS SCORE & SERUM ALBUMIN

The Pearson Correlation Coefficient of the correlation between serum albumin and the Glasgow Coma Scale score at admission, 0.612, is statistically significant ($p<0.05$). This shows that there is strong positive correlation between serum albumin value and the GCS at admission. So higher the serum albumin value, better the GCS.

GCS & SSS SCORE

The correlation between GCS and SSS score has a Pearson Correlation Coefficient of 0.859, which is statistically significant ($p < 0.05$). This implies a strong positive correlation between the GCS score at admission and the SSS score at admission. This means that the Glasgow Coma Scale and The Scandinavian Stroke Scale go hand in hand in measuring the severity of stroke at admission.

GCS & MRS SCORE

The Pearson Correlation Coefficient for the correlation between GCS and MRS score is -0.845 which is statistically significant ($p < 0.05$). This suggests a strong negative correlation between the GCS at admission and the MRS score at 7days. So a higher GCS at admission is associated with a lower MRS score or a better outcome at 7days.

SERUM ALBUMIN & SSS SCORE

The correlation between serum albumin at admission and the SSS score at admission has a Pearson Correlation Coefficient of 0.558, which is statistically significant ($p<0.05$). So there is a strong positive correlation between the serum albumin at admission and the Scandinavian Stroke Scale score. A higher albumin value is therefore

associated with a less severe stroke, as a higher SSS score indicates a milder stroke.

SERUM ALBUMIN & MRS SCORE

The Pearson correlation coefficient for the correlation between serum albumin value at admission and the MRS score, -0.700, is statistically significant. So there is a strong negative correlation between the serum albumin level at admission and the Modified Rankin Scale at 7days. A lower MRS score indicates a milder disability and better outcome. Hence the higher the serum albumin level, the lower the MRS score and better the outcome.

SSS SCORE & MRS SCORE

The Pearson Correlation Coefficient for the correlation between the SSS score and MRS score is -0.865, which is statistically significant ($p<0.05$). So there is strong negative correlation between the SSS score at admission and the MRS score at 7days. This implies that higher the SSS score, lower the MRS score. That is, less severe the stroke at admission, better the functional outcome at 7days.

RESULTS

- ✓ Of the 100 patients included in the study, 54 were males ((54%)
- ✓ The mean age of the study population was 58.44 ± 14.42 years, the oldest being 85year old and youngest 29years.
- ✓ Majority (53%) had MCA infarct
- ✓ Rheumatic heart disease was the major comorbidity associated with young stroke
- ✓ Hypertension was the major comorbidity in older age group
- ✓ There was no significant association between serum albumin and age
- ✓ A significant association was observed between serum albumin and severity of stroke at presentation
- ✓ There was strong positive correlation between serum albumin and the Glasgow Coma scale at admission
- ✓ A strong negative correlation was found between serum albumin at admission and MRS score, indicating a strong association between serum albumin and the functional outcome at 7days
- ✓ There was also significant association between the severity of stroke at admission and the functional outcome at 7days.

DISCUSSION

Albumin has well established important functions in health. Animal studies have shown neuroprotective effect of albumin in ischemic stroke. But this has not been well studied in humans. Though there are quite a few studies from the western world, there are very few Indian studies in this regard.

Previous studies have concluded that in ischemic stroke, serum albumin is an independent predictor of outcome. The study by Gariballa et al[52] has observed that serum albumin concentration is a strong and independent predictor of mortality. Of the various markers of nutritional status used in this study, only serum albumin showed a significant and independent association with stroke outcome. Aptaker et al[53] found that serum albumin concentrations at admission were significantly related to the rate of medical complications and functional outcome in stroke.

Our study included 100 patients with ischemic stroke. This sample size was small compared to most of the multicentric studies conducted in the western world. But the study results were comparable to that of previous studies. Males comprised 54% of patients in our study which made the sex distribution similar to the study by Abubakar et al[54]. The

mean age of our patients was 58.44 ± 14.42 as compared to 57.68 ± 12.4 in this study.

Table 18: Comparison of mortality & outcome with other studies

Study	Sample size	Males	Mean age	Mortality	Poor outcome
Dziedzic et al[55]	759	49%	68.3	12.9%	36%
Abubakar et al	75	52%	57.68±12.4	17.3%	52%
Idicula et al	444		70.4±14.4	13%	
Our study	100	54%	58.44±14.42	25%	54%

	SERUM ALBUMIN	
STUDY	POOR OUTCOME	GOOD OUTCOME
Dziedzic et al	3.41	3.68
Reinhardt et al[58]	< 3.4	> 3.5
Our study	3.13	4.16

Table 19: Comparison of S.albumin & outcome in various studies

Our study found no significant association between serum albumin and age as opposed to the finding in the study by Idicula et al[56]. But the study by Abubakar et al supported our finding.

Our study revealed higher mortality and more number of patients with unfavourable outcome compared to the study by Dziedzic et al. This is probably because in the afore mentioned study, patients with SSS score < 25 were excluded as they would be nonambulatory. The study by Reinhardt et al has found that serum albumin levels of < 3.4 are associated with a high mortality of about 25%. This might explain the high mortality observed in our study.

Our study, as in the above mentioned studies, has come out with a significant association between serum albumin levels and the severity of acute ischemic stroke. There is also significant correlation between serum albumin level and the functional outcome at 7 days. We have also found out significant correlation between the severity of ischemic stroke at onset and the functional outcome at 7days.

Albumin has been considered as a measure of health and disease. Malnutrition, liver disease, renal disease etc. reduce serum albumin concentration. Catabolic state and neuroendocrine response that follow stroke alter the serum albumin concentration. Malnutrition also downregulates protein synthesis. Nutrition is thought to be the single most important factor regulating albumin synthesis. Having excluded patients with hepatic and renal disease from the study population, the

serum albumin concentration in our study is probably a reflection of the nutritional status and may be causally related to the increased morbidity and mortality after stroke.

A study by Mallemoggala et al[57] has found that recurrence of stroke also was high in patients with low levels of albumin compared to patients with high levels.

A phase 3 trial, ALBUMIN IN ACUTE ISCHEMIC STROKE TRIAL (ALIAS), was conducted by the National Institute of Neurological Disorders and Stroke (NINDS) sponsored by the University of Miami, to determine whether human albumin administered within 5 hours of symptom onset improves 3month outcome of subjects with acute ischemic stroke. The study has been terminated but the results are not yet available. More nutritional intervention studies are needed to prove beyond doubt that improving serum albumin concentration will improve clinical outcome.

CONCLUSION

- ✓ Though the risk of stroke increases with age, most of our patients were middle aged in the 40-60year age group.
- ✓ Smoking and hypertension are the most common modifiable risk factors associated.
- ✓ GCS is as good as SSS as a measure of stroke severity.
- ✓ There was no significant variation of serum albumin with age or sex.
- ✓ Severity of stroke at onset has a definite association with outcome.
- ✓ Serum albumin influences both stroke severity and outcome.
- ✓ Serum albumin being a marker of nutritional status, nutritional support may improve the functional outcome of acute ischemic stroke.

SUMMARY

OBJECTIVE

1. To measure the stroke severity at admission using Scandinavian Stroke Scale.

2. To assess the functional outcome of ischemic stroke on day 7 using Modified Rankin Scale.

3. To find out the association between serum albumin at admission and the functional outcome of ischemic stroke.

4. To find out the correlation between serum albumin level and severity of ischemic stroke.

METHODOLOGY

- Patients admitted with first ever ischemic stroke were screened with the aid of investigations.

- Those who met the exclusion criteria were omitted to obtain 100 subjects.

- Severity of stroke at admission was measured using Scandinavian Stroke Scale.

- Functional status on 7th day was assessed with the help of Modified rankin Scale
- Statistical analysis was done to find out the association and correlation between serum albumin value at admission and the severity as well as outcome.

RESULTS

- ✓ Of the 100 patients included in the study, 54 were males ((54%)
- ✓ The mean age of the study population was 58.44 ± 14.42 years, the oldest being 85year old and youngest 29years.
- ✓ Majority (53%) had MCA infarct
- ✓ Rheumatic heart disease was the major comorbidity associated with young stroke
- ✓ Hypertension was the major comorbidity in older age group
- ✓ There was no significant association between serum albumin and age
- ✓ A significant association was observed between serum albumin and severity of stroke at presentation

- ✓ There was strong positive correlation between serum albumin and the Glasgow Coma scale at admission
- ✓ A strong negative correlation was found between serum albumin at admission and MRS score, indicating a strong association between serum albumin and the functional outcome at 7days
- ✓ There was also significant association between the severity of stroke at admission and the functional outcome at 7days.

CONCLUSION

- ❖ Serum Albumin levels have significant association with the severity as well as short term functional outcome of ischemic stroke.
- ❖ Improving serum albumin levels may improve the functional outcome of acute ischemic stroke.

BIBLIOGRAPHY

1. Lamberti E, Ross L, Taub E, editors. Thieme atlas of anatomy: head and neuroanatomy. 1st ed.New York: Thieme; 2007. p. 176.

2. Stroke –Lawrence M. Brass M.D. p.216

3. Types of stroke. Joao Gomes and Ari Marc Wachsman. p.16

4. Cooke J. A Treatise on Nervous Diseases. Volume 1:apoplexy. London: Longman, Hurst, Rees, Orme and Brown,1820

5. Smith W. Latin-English Dictionary. London: William Clowes and Sons, 1855.

6. Tanner TH. A Manual of the Practice of Medicine.London: H. Renshaw,1854.

7. Allen B. The Natural History of the Chalybeat and Purging Waters of England, with their Particular Essays and Uses. Among which are treated at large the Apoplexy and Hypochondriacism. London: S. Smith and B. Walford, 1699

8. Thomas H. Diseases of the Cerebral Bloodvessels. In:Osier W. Principles and Practice of Medicine. Volume 7.Philadelphia: Lea and Febiger, 1907

9. Robinson N. A Discourse upon the Nature and Cause of Sudden Deaths. London: T. Warner, 1732

10. Osier W. Principles and Practice of Medicine, editions1-15. Edinburgh: D. Appleton and Co. (eds 1 ^/Philadelphia:Lea and Febiger (eds 5-15), 1892-1944.

11. Davison C, Davey-Smith G, Frankel S. Lay epidemiology and the prevention paradox: the implications of coronary candidacy for health education. Social Health Illness 1991;13:1-9

12. Cheyne J. Causes of Apoplexy and Lethargy: with observations upon the comatose diseases. London: Thomas Underwood, 1812.

13. Victor M. Adams and Victor's principles of neurology. Chapter 34: Cerebrovascular diseases.7th ed. New York: McGraw Hill; 2001. p. 829–31.

14. Cereda C, Carrera E. Posterior cerebral artery territory infarctions. Front Neurol Neurosci.2012;30:128–31.

15. Harrison's Principles of Internal Medicine. 18th edition. p.3270-3294

16. Heros R. Stroke: early pathophysiology and treatment. Stroke.1994;25:1877-1881.

17. Garcia JH, Liu K, Yoshida Y et al. Brain microvessels:factors altering their patency after the occlusion of a middle cerebral artery (Wistar rat). Am J Pathol 1994; 145:728-40.

18. Hademenos GJ, Massoud TF. Biophysical mechanisms of stroke. Stroke. 1997;28:2067-77

19. Garcia JH, Yoshida Y, Chen H et al. Progression from ischemic injury to infarct following middle cerebral artery occlusion in the rat. Am J Pathol 1993; 142:623-635

20. Siesjõ BK: Cell damage in the brain: a speculative synthesis. J Cereb Blood Flow Metab.1981; 1:115-185

21. Siesjo BK Free radicals and brain damage. Cerebrovasc Brain Metab Rev. 1989; 1:165-211

22. Hakim AM. Ischemic penumbra, the therapeutic window. Neurology. 1998;51(Suppl 3):S44-S46.

23. Wise RJ, Bernardi S, Frackowiak RS, Legg NJ, Jones T. Serial observations on the pathophysiology of acute stroke: the transition form ischaemia to infarction as reflected in regional oxygen extraction. Brain. 1983;106 (Pt 1):197-222.

24. Choi DW. Ischemia-induced neural apoptosis. Curr Opin Neurobiol. 1996;6:667-672

25. Schwab S, Spranger M, Aschoff A, et al. Brain temperature monitoring and modulation in patients with severe MCA infarction. Neurology. 1997;48:762-767.

26. Derdeyn CP. Mechanisms of ischemic stroke secondary to large arter atherosclerotic disease.Neuroimaging Clin N Am. 2007;17(3):303–11. vii–viii.

27. Arenillas JF, Alvarez-Sabín J. Basic mechanisms in intracranial large- artery atherosclerosis:advances and challenges. Cerebrovasc Dis. 2005;20 Suppl 2:75–83.

28. Challa V. Atherosclerosis of the Cervicocranial arteries. In Toole JF (ed) Cerebrovascular disorders. 5th edition. Lippincott Williams and Wilkins, Philadelphia, 1999.

29. Luitse MJ, Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. Lancet Neurol. 2012;11(3):261–71

30. Chung EM, Hague JP, Chanrion MA, Ramnarine KV, Katsogridakis E, Evans DH. Embolustrajectory through a physical replica of the major cerebral arteries. Stroke. 2010;41(4):647–52

31. Takahashi K, Kobayashi S, Matui R, Yamaguchi S, Yamashita K. The differences of clinical parameters between small multiple ischemic lesions and single lesion detected by diffusion weighted MRI. Acta Neurol Scand. 2002;106(1):24–9.

32. Rapp JH, Pan XM, Yu B, Swanson RA, Higashida RT, Simpson P, et al. Cerebral ischemia and infarction from atheroemboli <100 micron in size. Stroke. 2003;34(8):1976–80

33. Lyden PD, Zivin JA. Hemorrhagic transformation after cerebral ischemia:Mechanisms and incidence. Cerebrovasc Brain Metab Rev.1993; 5:1-16.

34. Hart RG, Easton JH. Hemorrhagic infarcts. Stroke 1986;17: 586-89

35. Toni D, Fiorelli M, Bastianello S, Et al. Hemorrhagic transformation of brain infarct: predictability in the first five hours from stroke onset and influence on clinical outcome. Neurology. 1996;46:341-345.

36. Garcia JH, Anderson ML: Circulatory disorders and their effects on the brain.pp 715-822. In Davis RL, Robertson DM (eds): Textbook of Neuropathology, 3rd edition. Williams & Wilkins, Baltimore 1997

37. Mangla R, Kolar B, Almast J, Ekholm SE. Border zone infarcts: pathophysiologic and imaging characteristics. Radiographics. 2011;31(5):1201–14.

38. Paciaroni M, Agnelli G, Caso V, Bogousslavsky J, editors. Manifestations of stroke. Front Neurol Neurosci. Basel: Karger; 2012. 30:181–184

39. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey SmithG. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study [published correction appears in *BMJ*. 2006;333:468]. BMJ.2006;333:22.

40. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008;300:2142–2152.

41. Bonita R, Duncan J, Truelsen T, Jackson RT, Beaglehole R .Passive smoking as well as active smoking increases the risk of acute stroke. Tob Control. 1999;8:156–160.

42. Grundy SM. Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol. 2006;47:1093–1100.

43. Peters TJ. Metabolism: Albumin in the body. In : All about Albumin, Biochemistry, Genetics and Medical Applications. San Diego: 1996:188-250

44. De Feo P, Gaisano MG, Haymond MW. Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. J Clin Invest1991;88:833-840

45. Princen JMG, Mal-Basks GRB, Yap SH. Restoration effects of glucose refeeding on reduced synthesis of albumin and total protein on disaggregated polyribosomes in liver of starved rats: evidence of post-transcriptional control mechanism. Ann Nutr Metab 1983;27:182-193

46. Perlmutter DH, Dinarello CA, Punsal PI, Colten HR. Cachectin/ TNF regulates hepatic acute phase gene expression. J Clin Invest1986;78:1349-54

47. J.P.Nicholson, M.R. Wolmarans, G.R.Park. The role of Albumin in Critical Illness. Br J Anaesth 2000;85:599-610

48. Sapijasko MJA, Brant R, Sandham D, Berthiame Y. Non-respiratory predictor of mechanical ventilation dependency in ICU patients. Crit care Med 1996;24:601-607

49. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG et al.The APACHE III prognostic system.Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619-36

50. Sanchez R. Role of Albumin in burnt patients. Ann Fr Anaesth Reanim1996;15:1124-9

51. Tullis JL. Albumin I. Background and use. J Am Med Assoc1977; 237:355-9

52. Salah E. Gariballa et al. Influence of nutritional status on clinical outcome after acute stroke. Am J Clin Nutr 1998;68:275-81

53. Aptaker RL, Roth EJ, Reichhardt G et al.Serum albumin level as a predictor of geriatric stroke rehabilitation outcome. Arch Phys Med Rehabil 1994;75:80-4

54. Sani Abubakar, Anas Sabir et al. Low admission serum albumin as prognostic determinant of 30day case fatality and adverse functional outcome following acute ischemic stroke.Pan Afr Med J 2013;14:53

55. Dzeidzic et al. Serum Albumin level as a predictor of ischemic stroke and outcome.Stroke 2004;35(6):156-8

56. Idicula TT et al. Serum albumin in ischemic stroke patients-the higher the better-The Bergen stroke study.Cerebrovasc. Dis.2009;28(1):13-7

57. Mallemoggala Sai Babu et al.Serum albumin levels in ischemic stroke and its subtypes-correlation with clinical outcome. J Nutr 2012

58. Reinhardt GF, Myscofski JW, Stannard RT et al. Incidence and mortality of hypoalbuminemic patients in hospitalized veterans. J Parenter Enteral Nutr 1980;4:357-9

DEPARTMENT OF MEDICINE, CMC

PROFORMA

STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

Case No :

NAME :

AGE/ SEX :

IP NUMBER :

ADDRESS :

PHONE NUMBER :

PRESENTING COMPLAINTS:

- **Weakness**
- **Seizures**
- **Giddiness**
- **Unresponsiveness**
- **Unsteadiness of gait**
- **Deviation of angle of mouth**

DURATION OF SYMPTOMS :

H/o FEVER/ TRAUMA

PAST HISTORY :

- **Prior stroke**
- **Diabetes mellitus**
- **Hypertension**
- **Cardiac disease**
- **Epilepsy**
- **Tuberculosis**

TREATMENT HISTORY:

FAMILY HISTORY:

ADDICTIONS :

VITALS : Pulse- Rate & Rhythm

Blood Pressure

Respiratory Rate

Temperature

GENERAL EXAMINATION :

SYSTEMIC EXAMINATION

CENTRAL NERVOUS SYSTEM

- **Higher Mental Functions : Consciousness**

  Orientation

  Speech

- **Cranial Nerves**

- **Motor system : Tone**

  Power

  Reflexes

- **Sensory system**

- **Cerebellar signs**

- **Meningeal signs**

GLASGOW COMA SCALE : E V M Total score : /15

SCANDINAVIAN STROKE SCALE SCORE :

CARDIOVASCULAR SYSTEM

- **Apex Beat**
- **Heart sounds**
- **Murmurs**

RESPIRATORY SYSTEM :

- **Breath sounds**
- **Added sounds**

GASTROINTESTINAL SYSTEM

- **Any tenderness**
- **Liver span**
- **Shifting dullness**

INVESTIGATIONS

- **Complete hemogram**
- **Random Blood Sugar**
- **Blood urea**

- **Serum creatinine**
- **Liver function tests**
- **Lipid profile**
- **Serum proteins : Total :**

Albumin :

- **Urine routine examination : Albumin:**

Casts:

Cells:

- **ECG :**
- **CT scan Brain :**
- **MODIFIED RANKIN SCALE SCORE :**

(on the 7th day)

CONSENT FORM

Mr/Mrs/Ms……,

…….(relationship) of……(legal guardian) is being asked to be a participant in the research study titled **"STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE"** in CMC Hospital, Coimbatore, conducted by **Dr.REETA JAMES,** Post Graduate Student in the Department of General Medicine, Coimbatore Medical College. He /she satisfies eligibility as per the inclusion criteria. You/legal guardian can ask any question you may have before agreeing to participate.

Research Being Done

STUDY OF SERUM ALBUMIN AS A PREDICTOR OF SHORT TERM FUNCTIONAL OUTCOME IN ACUTE ISCHEMIC STROKE

Purpose of Research

Aim of the study is to find out the association of serum albumin at admission with severity of stroke & functional outcome on day 7.

Procedures involved

. It includes details like age,sex and history of diabetes, hypertension & symptoms suggestive of renal or liver disease and infection as well as clinical examination.

Investigations includes complete hemogram, renal function tests(blood urea, serum creatinine), blood sugar, lipid profile ,liver function tests, serum proteins, urine routine examination, electrocardiogram & CT scan Brain.

Decline from Participation

You have the option to decline from participation in the study existing protocol for your condition.

Privacy and Confidentiality

Privacy of individuals will be respected and any information about you or provided by you during the study will be kept strictly confidential.

Authorization to publish Results

Results of the study may be published for scientific purposes and/or presented to scientific groups, however you will not be identified.

STATEMENT OF CONSENT

I volunteer and consent to participate in this study. I have read the consent or it has been read to me. The study has been fully explained to me, and I may ask questions at any time.

---------- ----------

Signature /Left thumb impression Date

(volunteer)

---------- ----------

Signature of witness Date

ஒப்புதல் படிவம்

பெயர் :

பாலினம் : வயது :

முகவரி :

அரசு கோவை மருத்துவக் கல்லூரியில் பொது மருத்துவ துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவி **டாக்டர். ரீத்தா ஜேம்ஸ்** அவர்கள் மேற்கொள்ளும் **"கடுமையான இரத்தப் பக்கவாதத்தின் குறுகிய கால செயல்பாட்டு விளைவுகளை முன்னோகிப்பானாகிய சீரம் ஆல்புமின் பற்றிய ஆய்வு"** குறித்த ஆய்வில் செய்முறை மற்றும் அனைத்து விவரங்களையும் கேட்டுக் கொண்டு எனது சந்தேகங்களை தெளிவுப்படுத்திக் கொண்டேன் என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் இந்த ஆய்வில் முழு சம்மதத்துடன், சுய சிந்தனையுடனும் கலந்து கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வில் என்னுடைய அனைத்து விபரங்கள் பாதுகாக்கப்படுவதுடன் இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதை தெரிவித்துக் கொள்கிறேன். எந்த நேரத்தில் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : கையொப்பம் / ரேகை

நாள் :

MASTER CHART

Sl.No.	NAME	AGE	SEX	LESION	GCS	S. ALBUMIN	SSS SCORE	STROKE SEVERITY	MRS SCORE	DISABILITY	COMORBID CONDITIONS	ADDICTIONS
1	ACHIATHAL	70	F	1	5	4.2	6	SEVERE	6	DEATH	A	N
2	NANJAMMAL	70	F	4	14	4.2	30	MODERATE	4	MODERATE	A	S
3	KALIYAMMAL	60	F	2	11	3.6	32	MODERATE	4	MODERATE	A,B	S
4	KAVERI	70	F	1	5	4.2	10	SEVERE	5	SEVERE	A,B,C	N
5	SUBBULAKSHMI	55	F	1	9	3.2	14	SEVERE	5	SEVERE	E	N
6	KANNAMMAL	85	F	2	6	2.6	4	SEVERE	6	DEATH	D	S
7	KALIYAMMAL	63	F	2	15	4.2	26	MODERATE	4	MODERATE	A	N
8	PASUPATHY	58	F	1	9	4.1	20	SEVERE	5	SEVERE	E	N
9	PAPPATHY	85	F	1	5	3.8	2	SEVERE	6	DEATH	A,C	N
10	SELVI	37	F	1	7	2.7	12	SEVERE	6	DEATH	F	N
11	SABIYABEE	80	F	2	13	4.6	46	MILD	1	MILD	B	N
12	DHANALAKSHMI	70	F	1	12	4	48	MILD	2	MILD	D	N
13	LAKSHMI	40	F	1	5	3	2	SEVERE	6	DEATH	F	N
14	VIJAYALAKSHMI	57	F	1	15	4.2	49	MILD	1	MILD	E	N
15	KALPANA	41	F	1	9	4.8	15	SEVERE	4	MODERATE	E	N
16	MANICKAM	50	M	1	9	3	15	SEVERE	5	SEVERE	A	S
17	KARUPPUSAMY	83	M	1	5	2.7	2	SEVERE	6	DEATH	D	S
18	SANKARAPPAN	60	M	1	8	3.4	10	SEVERE	5	SEVERE	A	N
19	MURUGAN	65	M	1	9	4	11	SEVERE	5	SEVERE	A,C	S,L
20	KUMAR	39	M	3	14	4.3	42	MODERATE	3	MILD	A,D	S
21	AKBAR ALI	50	M	1	11	3.8	24	SEVERE	4	MODERATE	D	L
22	MURUGESAN	50	M	1	12	3.4	44	MILD	2	MILD	A	N
23	KANTHASAMY	64	M	3	5	2.4	2	SEVERE	6	DEATH	A	L

24	BASAVANNA	45	M	2	12	4.2	33	MODERATE	3	MILD	A,B	S
25	KRISHNASAMY	55	M	1	4	2.6	2	SEVERE	6	DEATH	B	N
26	PHILIP	75	M	1	9	4	15	SEVERE	4	MODERATE	D	N
27	SULAIMAN	60	M	1	6	4.7	16	SEVERE	5	SEVERE	A,B	S
28	CHINNAPPAN	68	M	4	9	4.2	31	MODERATE	4	MODERATE	A,B	L
29	SUNDARARAJ	41	M	1	5	2.7	2	SEVERE	6	DEATH	A,B	S
30	VELUMANI	45	M	4	8	4.1	31	MODERATE	4	MODERATE	D	L
31	MOORTHY	42	M	4	7	4.4	30	MODERATE	4	MODERATE	A	S
32	MURUGAN	40	M	1	13	4.4	41	MODERATE	2	MILD	B,D	L
33	DHANDAPANI	68	M	4	12	4.5	39	MODERATE	3	MILD	D	N
34	RAJAN	45	M	4	15	4.6	46	MILD	1	MILD	A	N
35	ALAGIN	79	M	4	8	3	15	SEVERE	5	SEVERE	C	N
36	IYYAMMAN	45	M	1	9	2.1	42	MODERATE	5	SEVERE	E	S
37	BABU	43	M	1	5	2.8	2	SEVERE	6	DEATH	A	S
38	MARATHAL	70	F	1	5	3.2	2	SEVERE	6	DEATH	B	N
39	JAYALAKSHMI	43	F	1	6	3	2	SEVERE	6	DEATH	A,B	N
40	VALLIAMMAL	85	F	2	9	3.1	41	MODERATE	5	SEVERE	A,B	S
41	SEETHALAKSHMI	70	F	4	6	3.6	2	SEVERE	6	DEATH	A	N
42	RANGAMMAL	65	F	4	9	4.8	15	SEVERE	4	MODERATE	A	N
43	MANICKAMMAL	84	F	1	5	3.4	2	SEVERE	6	DEATH	A	N
44	MARUTHATHAL	85	F	1	5	2.6	2	SEVERE	6	DEATH	E	N
45	PARVATHY	70	F	1	10	4.1	40	MODERATE	3	MILD	E	N
46	PAPPAL	74	F	1	9	4.1	16	SEVERE	4	MODERATE	A	N
47	VEERAMMAL	70	F	4	7	3.2	34	MODERATE	4	MODERATE	A	N
48	BHAGYALAKSHMI	54	F	4	12	4.6	33	MODERATE	4	MODERATE	A,B,C	N
49	PAPPATHIAMMAL	65	F	4	11	2.8	29	MODERATE	5	SEVERE	A	N
50	AKBAR	59	M	4	9	4.5	39	MODERATE	1	MILD	A	S

Sl.No.	NAME	AGE	SEX	LESION	GCS	S. ALBUMIN	SSS SCORE	STROKE SEVERITY	MRS SCORE	DISABILITY	COMORBID CONDITIONS	ADDICTIONS
51	NAGARAJ	56	M	4	7	3.2	19	SEVERE	5	SEVERE	A	S
52	SARASWATHY	57	F	1	6	3.4	14	SEVERE	5	SEVERE	A,B	N
53	SURESHKUMAR	30	M	1	5	2.6	2	SEVERE	6	DEATH	A,B,D	S,L
54	VIVEKANANTHAM	39	M	1	9	4	34	MODERATE	4	MODERATE	D	S
55	VAIRAMUTHU	43	M	1	9	4.1	21	SEVERE	4	MODERATE	B	S
56	MOHAMMED USUF	72	M	4	8	3.9	20	SEVERE	4	MODERATE	A	N
57	KALAVATHY	44	F	1	5	2.2	2	SEVERE	6	DEATH	B,D	N
58	MATHAYAN	60	M	3	6	3.6	4	SEVERE	5	SEVERE	A	S
59	BABU	38	M	1	9	4	10	SEVERE	5	SEVERE	C	S
60	AMSAVENI	34	F	1	10	4.2	30	MODERATE	5	SEVERE	A,D	N
61	PHILOMINA	65	F	2	12	4.2	36	MODERATE	4	MODERATE	A	N
62	AYSHABEEVI	80	F	2	5	3	2	SEVERE	6	DEATH	A	N
63	HALAMMAL	70	F	2	5	2.8	2	SEVERE	6	DEATH	A	N
64	CHANDRA	37	F	1	11	4.2	29	MODERATE	3	MILD	F	N
65	PONNUSAMY	52	M	1	12	4.6	33	MODERATE	2	MILD	A,D	N
66	ARUMUGATHAI	70	F	4	9	3.6	20	SEVERE	5	SEVERE	D	S
67	THIRUMAN	72	M	2	8	3.4	12	SEVERE	5	SEVERE	D	S
68	PALANIYAMMAL	60	F	4	10	4.1	23	SEVERE	4	MODERATE	E	N
69	CHINNAMANI	55	F	2	11	4.2	29	MODERATE	3	MILD	B,D	N
70	PAPPATHY	60	F	1	9	3.7	20	SEVERE	4	MODERATE	D	N
71	MANJULA	46	F	1	9	3.8	15	SEVERE	4	MODERATE	B,D	N
72	LAKSHMI	85	F	2	5	2.6	2	SEVERE	6	DEATH	E	N
73	NAGENDRAN	57	M	4	10	4	26	MODERATE	4	MODERATE	A,B	L
74	NEHRU	42	M	2	13	4.2	38	MODERATE	3	MILD	A,C	S

75	GOPAL	40	M	3	14	4.8	41	MODERATE	2	MILD	D	S
76	VANAJA	50	F	4	9	3.1	14	SEVERE	5	SEVERE	A	N
77	PETHAI	60	F	2	6	4	24	SEVERE	5	SEVERE	A	S
78	VIJAYA	60	F	1	6	3.4	14	SEVERE	5	SEVERE	A,B	N
79	SUBBAN	60	M	1	10	3.1	30	MODERATE	4	MODERATE	A	S
80	GANAPRAKASH	40	M	1	13	4.2	39	MODERATE	3	MILD	A,B	S
81	KUPPUSAMY	63	M	1	9	3	32	MODERATE	5	SEVERE	A,D	L
82	RAMAIAH	68	M	4	5	2.4	2	SEVERE	6	DEATH	A,B	N
83	RAYAPPAN	64	M	1	6	2.1	4	SEVERE	5	SEVERE	A	N
84	THAVASUMUTHU	67	M	4	4	2.2	2	SEVERE	6	DEATH	A	S
85	CHELAMANI	45	M	1	13	4	41	MODERATE	3	MILD	C,D	N
86	SUBBAIAH	75	M	1	7	3.7	24	SEVERE	5	SEVERE	A	L
87	THANGAVEL	63	M	3	9	4.2	21	SEVERE	4	MODERATE	D	S
88	MURALIDHARAN	35	M	1	11	2.8	29	MODERATE	5	SEVERE	B,D	S
89	VELUMAYIL	60	M	2	5	3	2	SEVERE	6	DEATH	A	S,L
90	RANGASAMY	72	M	4	8	2.1	30	MODERATE	5	SEVERE	A,B	S
91	NAMMALVAR	67	M	4	12	4.6	40	MODERATE	3	MILD	A	L
92	AMOSE	53	M	1	14	4.4	41	MODERATE	3	MILD	D	S
93	ASHOKRAJ	29	M	1	12	4	39	MODERATE	3	MILD	A,D	S
94	KANDAN	50	M	4	12	4.1	41	MODERATE	3	MILD	D	S
95	VISWANATHAN	65	M	1	10	3	16	SEVERE	5	SEVERE	A,B	L
96	MUTHAN	75	M	2	4	4	2	SEVERE	6	DEATH	D	S
97	SHANTHI	35	F	1	14	4.4	43	MILD	2	MILD	F	N
98	BALASUBRAMANIAM	52	M	1	5	2.7	2	SEVERE	6	DEATH	A	N
99	KANNAMMAL	70	F	2	9	2.8	18	SEVERE	5	SEVERE	A	S
100	GANDHIMATHI	55	F	4	6	3	24	SEVERE	5	SEVERE	A	N

KEY TO MASTERCHART

1: MCA Infarct

2: Multiinfarct

3: PCA/ Posterior circulation stroke

4: Lacunar stroke

A : Systemic Hypertension

B: Diabetes Mellitus

C: Coronary Artery Disease

D : Dyslipidemia

E: Nil

F: Rheumatic Heart Disease

S: Smoking/ Tobacco chewing

L: Alcohol

N:Nil

SEVERITY GRADING	MILD	MODERATE	SEVERE	DEATH
MRS	0-3	4	5	6
SSS	43-58	26-42	0-25	--